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185-26117
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TIR 2114-MED-5015

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CONTRACT NO:

NAS9-17151

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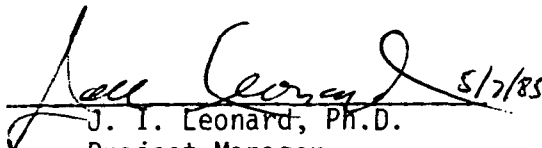
DRL T-1825

DRD MA945T

SUBJECT

Final Report - Contract NAS9-17151
Computer Simulation Studies in Fluid and Calcium
Regulation and Orthostatic Intolerance


The attached Final Report is submitted in response to Contract NAS9-17151, DRL T-1825. This report summarizes the results of all work performed under this contract and references the respective reports (TIR's) satisfying each task item specified in the contract.


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COMPUTER SIMULATION STUDIES IN FLUID AND CALCIUM
REGULATION AND ORTHOSTATIC INTOLERANCE

FINAL REPORT
CONTRACT NAS9-17151

Prepared for

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

Prepared by

Management and Technical Services Company
Houston, Texas

May 7, 1985

TABLE OF CONTENTS

<u>Section No.</u>	<u>Title</u>	<u>Page</u>
1.0	<u>INTRODUCTION</u>	1
2.0	<u>BODY FLUID AND BLOOD VOLUME REGULATION</u>	4
2.1	INTRODUCTION	4
2.2	APPROACH	5
2.3	RESULTS	7
	2.3.1 <u>Fluid/Electrolyte Regulation</u>	7
	2.3.2 <u>Erythropoietic Regulation</u>	18
2.4	CONCLUSIONS	24
3.0	<u>ORTHOSTATIC INTOLERANCE AND CARDIOVASCULAR DECONDITIONING</u>	31
3.1	INTRODUCTION	31
3.2	APPROACH	32
3.3	RESULTS	32
	3.3.1 <u>Review of the Literature</u>	32
	3.3.2 <u>Cardiovascular Response During Shuttle Reentry</u>	33
	3.3.2 <u>Countermeasures for Orthostatic Intolerance</u>	34
3.4	CONCLUSIONS	36
4.0	<u>CALCIUM REGULATION AND BONE ATROPHY</u>	39
4.1	INTRODUCTION	39
4.2	APPROACH	41
4.3	RESULTS	43
4.4	CONCLUSIONS	51

TABLE OF CONTENTS (Continued)

<u>Section No.</u>	<u>Title</u>	<u>Page</u>
5.0	<u>POTENTIAL CONTRIBUTIONS OF PHYSIOLOGIC MATH MODELS TO FUTURE FLIGHT EXPERIMENTS</u>	53
5.1	EXPERIMENT A: MEASUREMENT OF VENOUS PRESSURES AND PLASMA VOLUME.	53
5.2	EXPERIMENT B: CIRCADIAN RHYTHM OF PLASMA HORMONES AND ELECTROLYTES DURING WEIGHT- LESSNESS	57
5.3	EXPERIMENT C: EARLY AND LONG DURATION EFFECTS OF WEIGHTLESSNESS ON SELECTED ENDOCRINE PARAMETERS IN PLASMA AND URINE: ANTIDIURETIC HORMONE, HUMORAL NATRIURETIC SUBSTANCES, CORTISOL . . .	57
5.4	EXPERIMENT D: EFFECTS OF WEIGHTLESSNESS ON ADRENAL AND KIDNEY INTERACTION	67
5.5	EXPERIMENT E: LONG-TERM EFFECTS OF INCREASED ELECTROLYTE AND MUSCLE LOSS ON RENAL FUNCTION	71
5.6	EXPERIMENT F: STUDY OF CORTICOSTEROID HORMONE METABOLISM IN WEIGHTLESSNESS BY USE OF PHARMACOLOGIC INTERVENTION.	72
5.7	EXPERIMENT G: EFFECT OF LOWER BODY NEGATIVE PRESSURE, WATER-SALT SUPPLEMENTS AND EXERCISE ON WEIGHTLESSNESS- INDUCED CHANGES IN ENDOCRINE AND ELECTROLYTE PARAMETERS	72
6.0	<u>REFERENCES</u>	75

COMPUTER SIMULATION STUDIES IN FLUID AND CALCIUM REGULATION AND ORTHOSTATIC INTOLERANCE

FINAL REPORT

1.0 INTRODUCTION

This is the final report for Contract NAS9-17151 which was in effect from May 7, 1984, to May 7, 1985, with the National Aeronautics and Space Administration. The statement of work for this contract is contained in Appendix A of this report and involves work in three major areas of physiological concern which have been subdivided into six tasks. Each of these tasks was accomplished and the work has been transmitted to NASA in twenty-three Technical Information Releases which are listed in Appendix B. Because of the detailed nature of these study reports, the present final report will only attempt to summarize the overall effort.

The thread that ties these tasks together is the systems analysis approach to physiological research, a theoretical approach that utilizes mathematical modeling and computer simulation as its major tools. These mathematical models and related data systems have been under development by NASA and the present contractor for a number of years under various contracts.* In addition to the development of operational models, an important part of the past and current effort has been in applying these models to the problems of space physiology. Specifically, they have proved to be valuable tools in integrating much of the data from space flight (Skylab) and ground-based tests. They have assisted in identifying the hypotheses and design of experiments which are currently being readied for flight, and they have provided insight into new approaches for crew health maintenance. A major focus has been the evolution of a multi-disciplined, integrated hypothesis for adaptation to the weightlessness environment (Figure 1-1).

* See references listed under "Final Report" (7-11).

An executive summary of this overall effort was completed and released during the current contractual period, "An Integrated Analysis of the Physiological Effects of Space Flight" (28). An additional document was also released that provides an introduction to modeling and simulation to those unfamiliar with this topic, "The Modeling and Simulation of Feedback Control Systems" (29).

This report is structured to correspond to the major areas of physiological concern delineated in the Statement of Work. Section 2.0 concerns Body Fluid and Blood Volume Regulation, Section 3.0 concerns Orthostatic Intolerance and Cardiovascular Deconditioning, Section 4.0 concerns Calcium Regulation and Bone Atrophy, and Section 5.0 concerns Potential Contributions of Physiologic Math Models to Future Flight Experiments. Each section references the applicable contract task numbers, as well as separately published study reports. Recommendations for future work are contained in each section as appropriate. As part of a related task, the contractor recently compiled a set of candidate flight experiment objectives for the life science disciplines. Inasmuch as systems analysis and mathematical modeling provided the organizing principles for generating this compilation, and because it is in accord with the contract task on experimental design, it has been included as Appendix C.

INTEGRATED HYPOTHESIS OF PHYSIOLOGICAL ADAPTATION TO PROLONGED SPACE FLIGHT

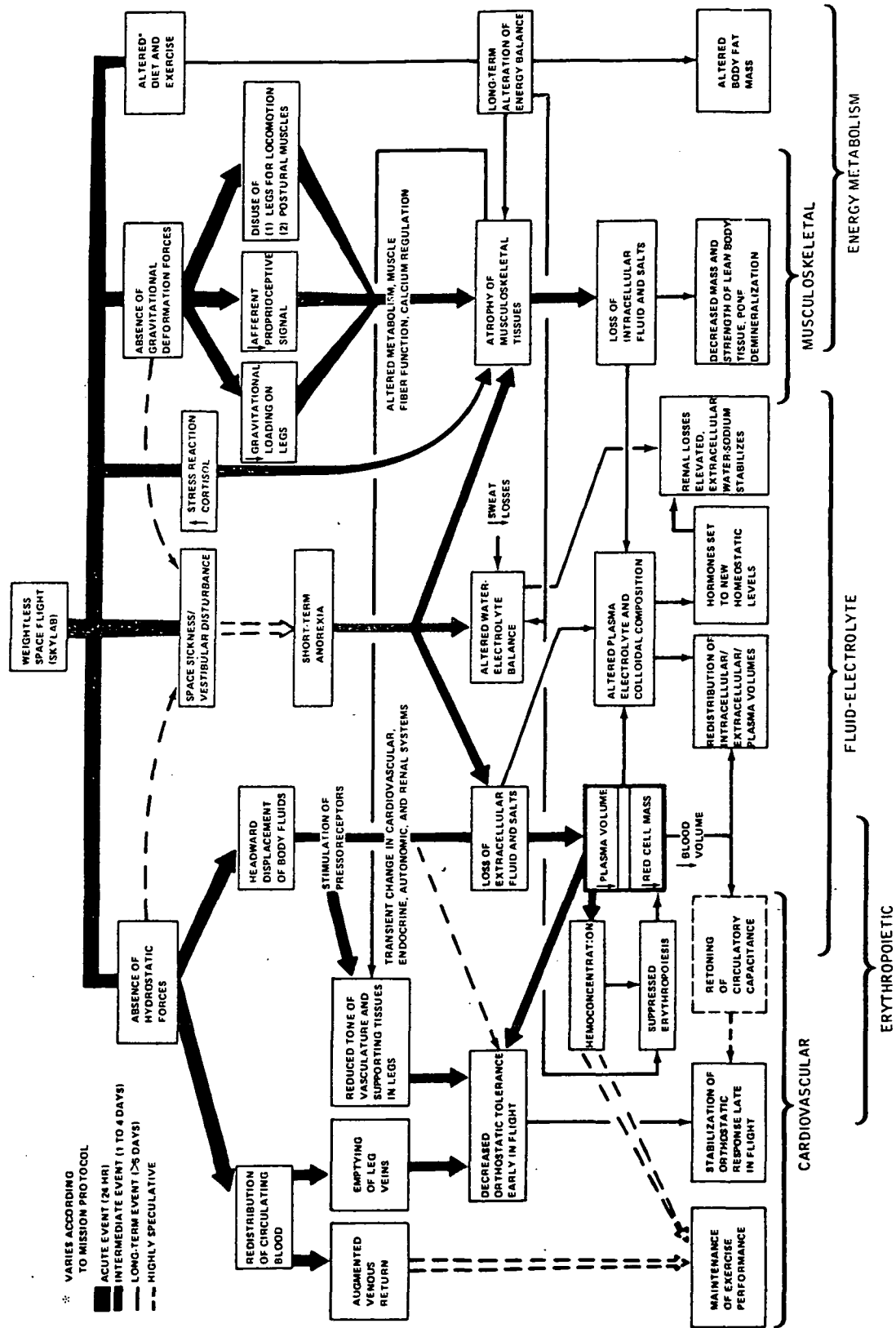


FIGURE 1-1

2.0 BODY FLUID AND BLOOD VOLUME REGULATION

There are two tasks in this area of physiological concern as delineated in the Statement of Work (See Appendix A).

Task 1 - Development of an Integrated Analysis of Blood Volume Regulation During Space Flight

Task 3 - Design of Key Experiments Related to Body Fluid and Blood Volume Regulation

Task 1 is addressed in this section, while the results of Task 3 are presented in Section 5.0.

2.1 INTRODUCTION

Central to an understanding of the overall physiological response to weightless exposure, is the elucidation of the physiologic mechanisms underlying the loss of blood volume during space flight. The factors responsible for the approximately 10 percent loss of blood volume observed in crewmembers returning from space, while not well understood, are believed to be a result of normal feedback processes involving circulatory, renal, endocrine, hematologic, and other related systems (32). Although never measured directly during flight, blood volume is believed to be reduced acutely, due to pure plasma volume loss which is followed by a more gradual loss of red cells (17). The result of this blood volume loss has important negative cardiovascular consequences in exercise and orthostatic performance^{*} (14). The etiology of the plasma volume loss is probably a response to headward fluid shifts and upper body circulatory volume overload. The actual metabolic routes of body-fluid loss may be a combination of disturbances in fluid intake, renal excretion, and perhaps under certain conditions, evaporative water loss, as well.

* These cardiovascular issues are addressed in more detail under Tasks 4 and 5 of this report.

However, in spite of the central role that blood volume plays in the space-flight response, and in spite of the large number of studies that have been devoted to measuring plasma volume or red-cell mass loss during water immersion, bed rest, and space flight, there has been no rigorous attempt to integrate the findings of these studies in the context of a unified theory of blood volume regulation. Blood volume regulation is typically discussed in terms of either plasma volume regulation, (that is, during dehydration, fluid loading, or orthostasis) or erythropoietic regulation (that is, during phlebotomy, hypoxia, or hemolytic anemia). Space flight, however, seems to affect, in a fundamental way, both of these systems. The overall blood volume regulation in weightlessness is the subject of Task 1 of the Statement of Work.

2.2 APPROACH

The lack of frequent opportunities for in-flight experimentation has created an emphasis on simulating space-flight effects by using ground-based experimental analogs of zero-g as well as by developing and using mathematical models. Water immersion studies in man and head-down tilt studies in both man and animals have been used to simulate short-term adaptation to weightlessness, while bed-rest studies have been used to simulate longer-term space-flight observations (12,18,37). Mathematical models, particularly those developed by the contractor, have successfully served to analyze and interpret these one-g analog studies, as well as the space-flight data (46).

Two models in particular, the Guyton model of fluid and electrolyte control (13), and the Leonard model of erythropoiesis control (20) have been used extensively in the analyses and interpretations of data related to space flight and its one-g analogs. The original Guyton model has been previously modified by this contractor to reflect new physiological developments and to allow the simulation of zero-g effects (19,45). This model and its modifications were developed by combining integrative and logical characteristics of homeostatic feedback theory with mathematical representations of the body's control systems. The erythropoiesis model was developed in support of NASA's hematology research program. This model

incorporates the most current understanding of the dynamics of red-cell production and the associated feedback regulation based on the balance between tissue oxygen supply and demand. Together, these two models provide the theoretical basis for a study of the total loss of blood volume during space flight and its analogs, including an analysis of the separate but related changes in plasma volume and red cell mass.

The fluid and electrolyte model based upon Guyton's work contains an excellent description of the regulation of plasma volume, but is incomplete with regard to its erythropoiesis-control algorithm. Therefore, the approach taken to complete this task was to incorporate the superior "stand-alone" model of erythropoiesis control with that of the modified Guyton model. This hybrid model, along with the stand-alone model of erythropoiesis, were used to perform a series of analyses designed to address the causes and consequences of blood volume regulation as it pertains to weightlessness. These analyses resulted in the preparation of eleven reports/presentations over the course of the contract period. These reports/presentations can be grouped into two major categories as listed below - those related to Fluid/Electrolyte Regulation, and those related to Erythropoiesis Regulation. They embody the essence of Task 1 and provide an integrated view of blood volume regulation.

A. Fluid/Electrolyte Regulation

Leonard, J. I. Mathematical Modeling of Fluid-Electrolyte Alterations During Weightlessness, TIR 2114-MED-4001. (24)

Leonard, J. I. Analysis of Head-Down Tilt as an Analog of Weightlessness Using a Mathematical Simulation Model, TIR 2114-MED-4003. (26)

Leonard, J. I. Fluid-Electrolyte Responses During Prolonged Space Flight: A Review and Interpretation of Significant Findings, (TIR 2115-MED-5008. (30)

Leonard, J. I. The Behavior of Renal-Regulation Hormones During Hypogravic Stress, TIR 2115-MED-5002. (31)

B. Erythropoietic Regulation

Leonard, J. I. Systems Analysis of the Erythropoietic Responses to Weightlessness- Vol. I.: Mathematical Model Simulations of the Erythropoietic Responses to Weightlessness, TIR 2114-MED-5003). (32)

Leonard, J. I. A Systems Analysis of the Erythropoietic Responses to Weightlessness, Vol II.: Description of the Model of Erythropoiesis Regulation, TIR 2114-MED-5004. (33)

Nordheim, A. W. A Detailed Analysis of the Erythropoietic Control System in the Human, Squirrel Monkey, Rat and Mouse, TIR 2114-MED-5010. (38)

Nordheim, A. W. Use of Modeling in Developing Experimental Protocols Appropriate for Space Flight Experiments, 1983. (39)

2.3 RESULTS

The following reports/presentations, grouped as shown above, were prepared in response to Task 1. Short abstracts of each report are presented below to provide a summary of the work performed, the type of information available, and how that information is related to the contract task.

2.3.1 Fluid/Electrolyte Regulation

- a) Leonard, J.I. Mathematical Modeling of Fluid-Electrolyte Alterations During Weightlessness, TIR 2114-MED-4001. (24)

This report concentrates on one particular discipline that has been intensively studied in weightlessness - the fluid/electrolyte metabolism and the renal-endocrine control of that system as it adapts to a new environment. The report defines the physiological system of interest and discusses the models that have been particularly useful (specifically, the Guyton model of circulatory, fluid, and electrolyte control) and the Leonard model of erythropoiesis control in examining that system. However, the main emphasis of the report is not on the details of the model or the simulation studies. Rather, the primary conclusions of the computer studies are examined in terms of their physiological meaning and in the context of achieving a better understanding of physiological behavior in weightlessness.

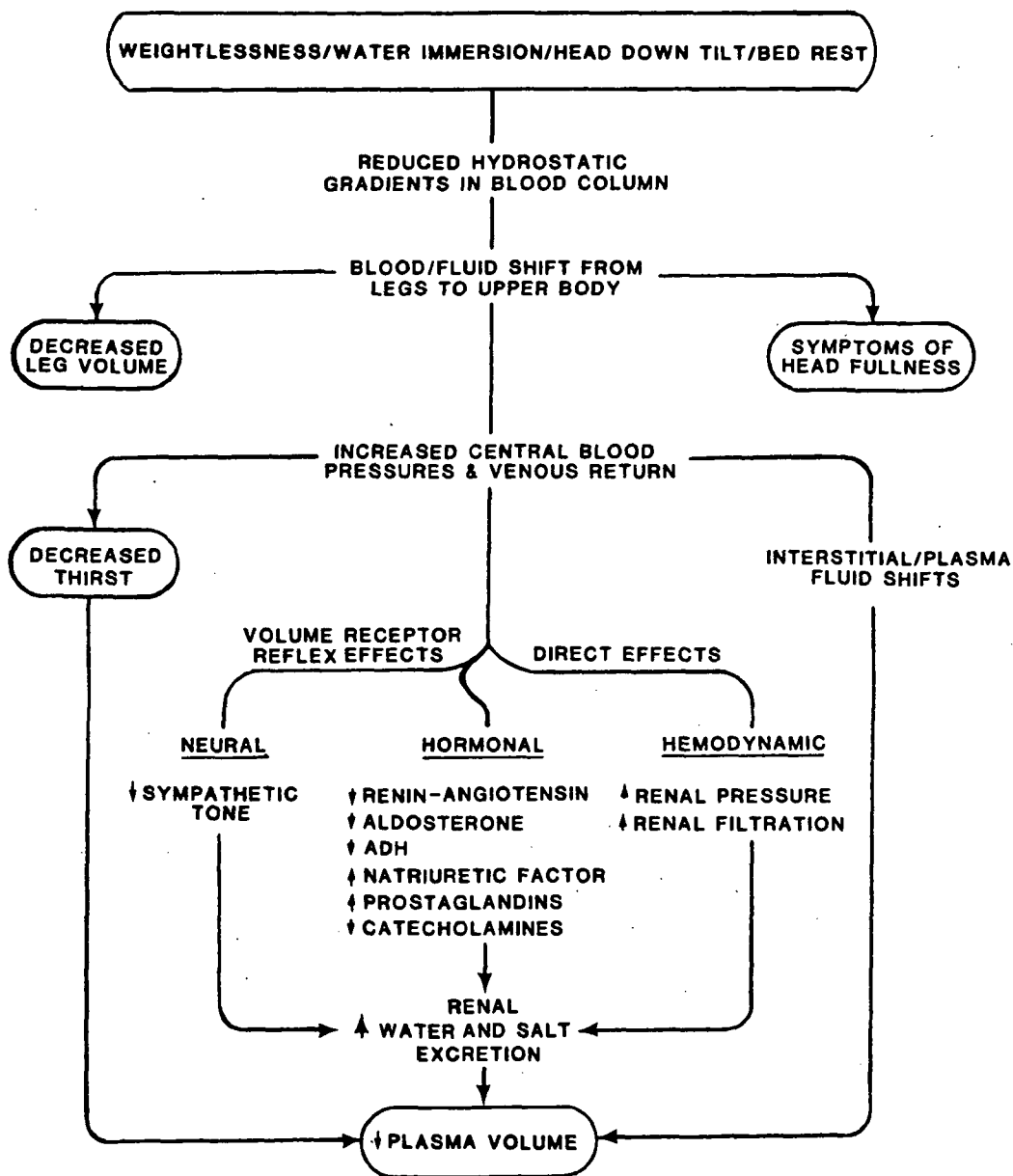
A discussion of the major ground-based analogs of weightlessness are included: for example, head-down tilt, water immersion, and bed rest, as well as a comparison of findings from those studies with space flight. Several important zero-g phenomena are described in detail, including acute fluid volume regulation, blood volume regulation, circulatory changes, longer-term fluid-electrolyte adaptations, hormonal regulation, and body composition

changes. Hypotheses are offered to explain the major findings in each area and these are integrated into a larger hypothesis of space-flight adaptation. These hypotheses are testable and have provided a basis for some of the next generation of space-flight studies concerning blood volume regulation during zero-g exposure. Figure 2-1 is an important example of an hypothesis that has been formulated as a result of modeling and awaits to be tested in space. It concerns the mechanisms of plasma volume loss in space flight and, therefore, represents an important portion of the overall zero-g blood volume regulatory theory. The remaining elements of the picture are discussed in the next subsection below. The report provides the conceptual foundation for the contractual tasks concerning fluid-electrolyte metabolism (Task 1 and 3), blood volume regulation (Task 1), and cardiovascular regulation (Tasks 4 and 5).

- b) Leonard, J.I. Analysis of Head-Down Tilt as an Analog of Weightlessness Using a Mathematical Simulation Model, TIR 2114-MED-4003. (26)

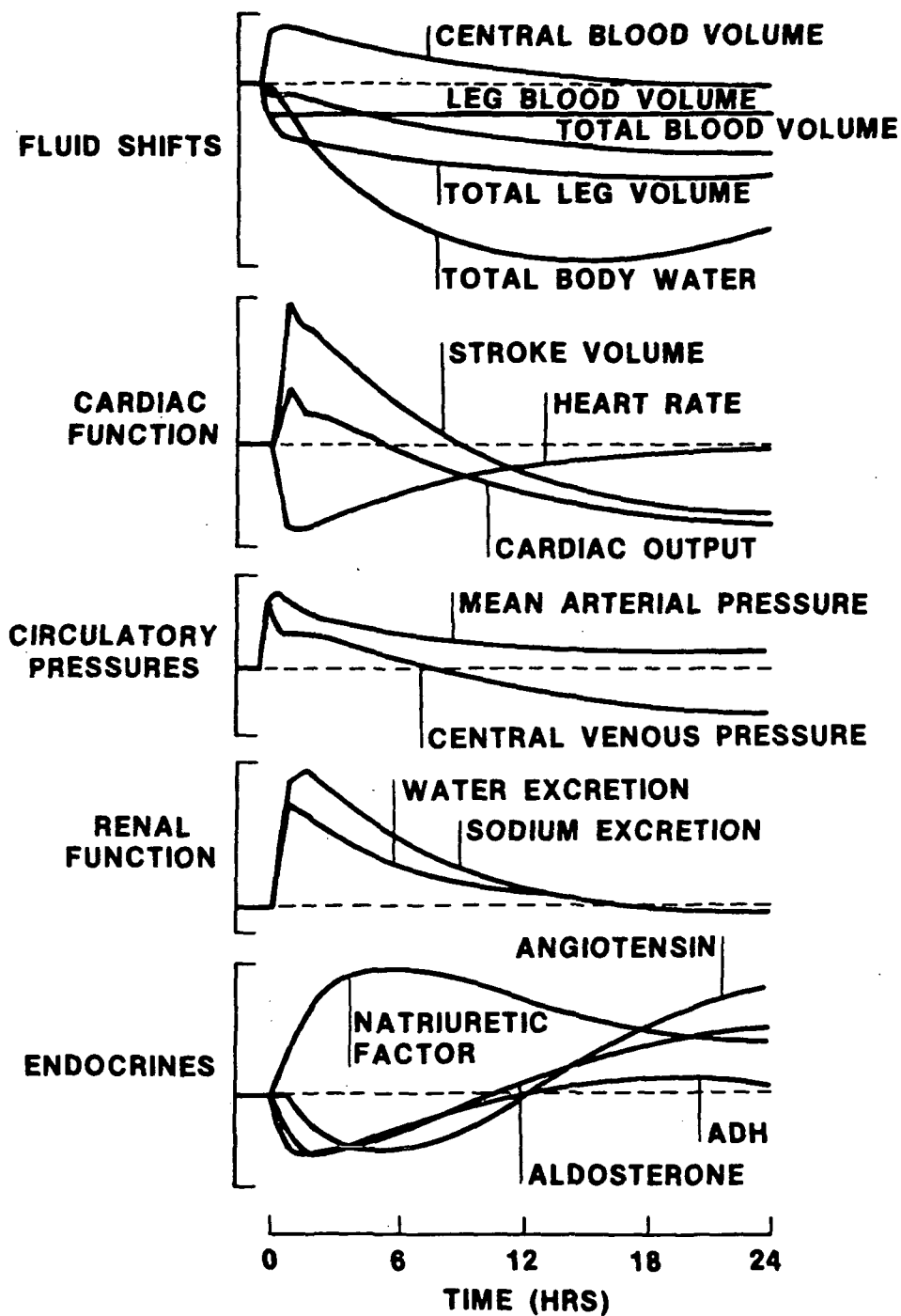
Anti-orthostasis or head-down tilt of a moderate degree has been used as a ground-based analog of weightless space flight to study headward fluid shifts, decreased plasma volume, orthostatic intolerance, and musculo-skeletal degradation. In this study, the modified Guyton model was used to help interpret the head-down tilt response and relate the elicited physiological changes to those which occur in space flight. By using the same mathematical model to simulate both space flight and ground-based experimental analogs of space flight, it is possible to test hypotheses regarding mechanisms and control systems, and thus, discern the major characteristics of these stresses, their similarities and differences.

Two different experimental studies were employed in this paper to validate the model. The first was a 24-hour -5° head-down tilt study (1,37) and the second was a 7-day -6° head-down bed rest study (47). The simulations of both of these studies demonstrated changes in the fluid volume, hemodynamic, electrolyte, hormone and renal characteristics that are in good agreement with direct experimental results. Figure 2-2 shows the results of a head down tilt simulation. The fluid-shift hypothesis of Figure 2-1 that explains the



FLUID - SHIFT HYPOTHESIS

FIGURE 2-1



SIMULATION OF HEAD DOWN TILT (-6°)

FIGURE 2-2

reduction in plasma volume was elucidated by studying model behavior as shown in Figure 2-2. This is an important simulation, because it represents a detailed prediction of the acute events of cardiovascular and fluid regulation during the first day of space flight. A number of flight experiments are currently being readied to examine this early period of weightlessness. The veracity of the model in its predictions is suggested by the good agreement between data and model behavior for head-down tilt, as shown in Table 2-1. Other issues which were addressed, included the dynamic changes of venous pressure and cardiac output, the extent of central hypervolemia during long term zero-g exposure, the existence of an early diuresis (which is yet to be measured), the mechanisms which alter the renal-regulating hormones during the short-term and long-term periods, the significance of potassium loss on other zero-g responses, and the role of transcapillary filtration in adjusting fluid shifts. This study illustrates the use of mathematical models as an interpretive and analysis technique for assisting experimental research for space life science.

- c.) Leonard, J.I. Fluid-Electrolyte Responses During Prolonged Space Flight: A Review and Interpretation of Significant Findings, TIR 2114-MED-5008. (30)

This document summarizes the most important results of the Skylab studies related to fluid-electrolyte regulation. These data became the starting point of an extensive systems analysis to study adaptation to the weightlessness environment. A brief summary of the systems analysis study, including an interpretation of Skylab results, is also included.

Most of the results contained in this document have been published by the Skylab principal investigators, but in a different format. New analyses of these data are presented, describing both the short and long-term responses to space flight. Developing a composite picture of these responses, based on the nine Skylab crewmen, was preferable in most instances to explaining the differences between flights. Therefore, instead of presenting the individual crew data for day-by-day biochemical changes in blood and urine (which has been previously reported), this information has been computed as daily nine-man averages so that trends, if they exist, can be more easily discerned. Figures 2-3 to 2-6 represent 9 crew-man averages of body water and electrolyte

TABLE 2-1

COMPARISON OF SIMULATION AND EXPERIMENTAL RESPONSE FOR 24-HOUR HEAD-DOWN (-5°) TILT STUDY

<u>QUANTITY</u>	<u>VALUE @ 24-HOURS COMPARED TO CONTROL</u>	
	<u>HEAD-DOWN TILT</u>	<u>MODEL</u>
FLUID SHIFTS		
TOTAL BODY WATER	-1300 ml	- 1130 ml
LEG BLOOD VOLUME	ND	- 256 ml
LEG INTERSTITIAL VOLUME	ND	- 454 ml
TOTAL LEG VOLUME	- 900 ml	- 710 ml
TOTAL BLOOD VOLUME	- 425 ml	- 563 ml
HEMATOCRIT	+ 7.5%	+ 12.5%
URINE RATE, 1ST 8 HR/24 HR	127%	190%
HEMODYNAMICS		
CARDIAC OUTPUT	- 7.8%	- 11.1%
STROKE VOLUME	- 8.5%	- 9.8%
HEART RATE	0%	1.4%
ARTERIAL PRESSURE	+ 3%	+ 3%
CENTRAL VENOUS PRESSURE	- 49%	- 9%
LEFT ATRIAL PRESSURE	ND	- 50%
PERIPHERAL RESISTANCE	+ 11.3%	+ 16.0%
HORMONES		
ANGIOTENSIN	+ 25%	+ 27%
ALDOSTERONE	+ 35%	+ 17%
ADH	+ 57%	+ 3%
NATRIURETIC FACTOR	ND	+ 13%

ND = NOT DETERMINED

BODY WATER AND ELECTROLYTE CHANGES DURING PROLONGED SPACEFLIGHT SKYLAB MEAN (N = 9)

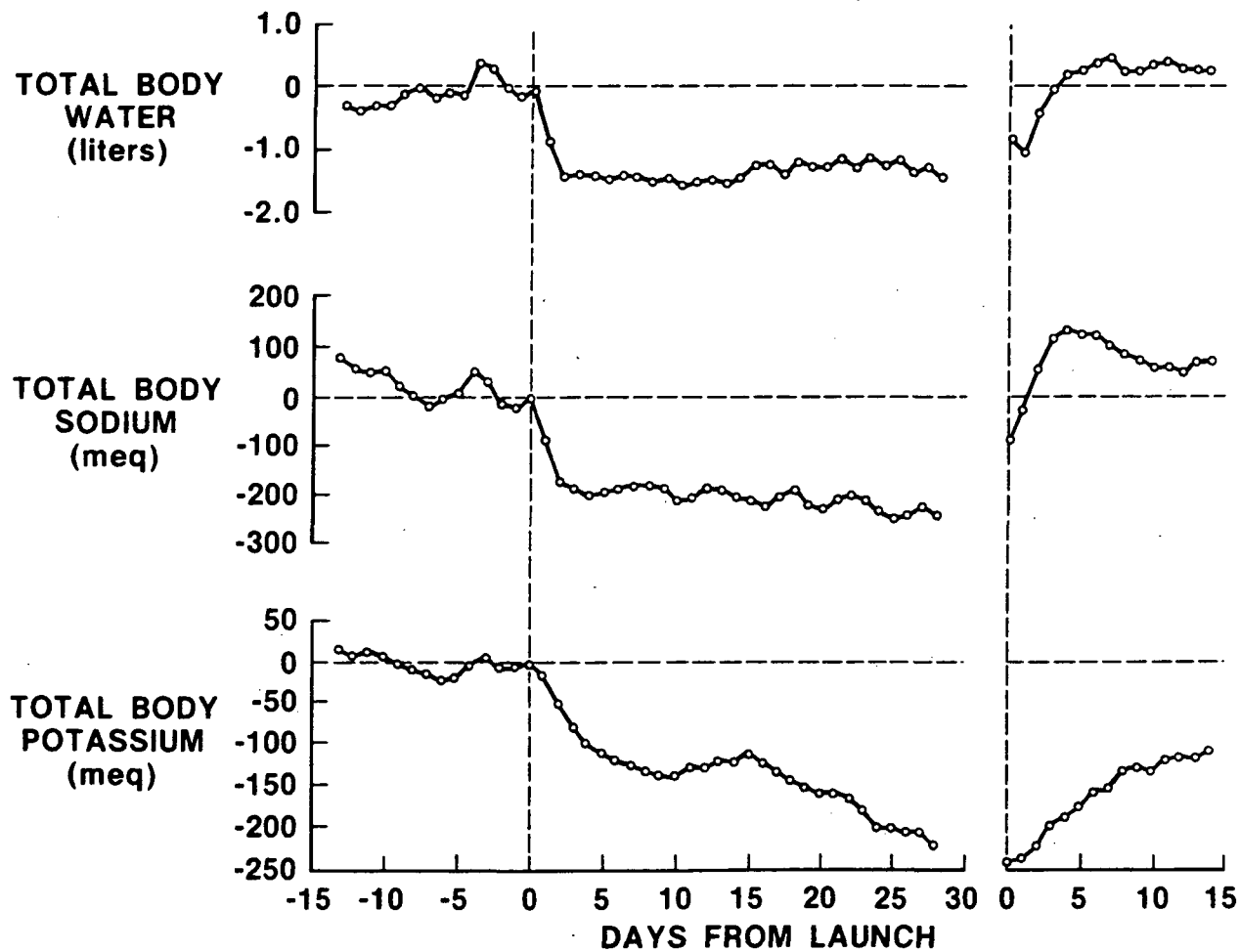


FIGURE 2-3

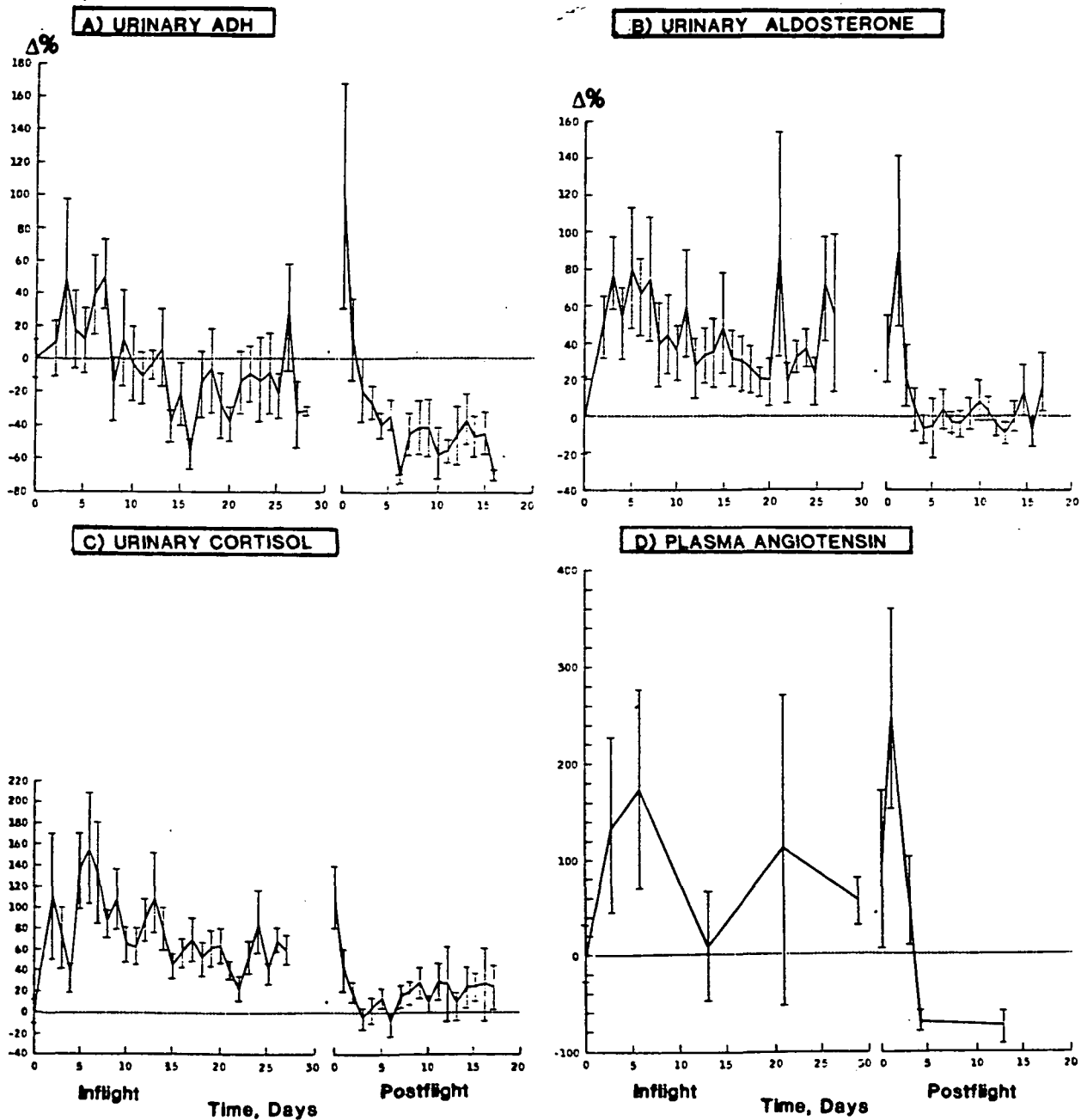


FIGURE 2-4

Hormonal Response of Skylab Crew during the first month inflight and the first two weeks postflight. Data from first mission day not available.

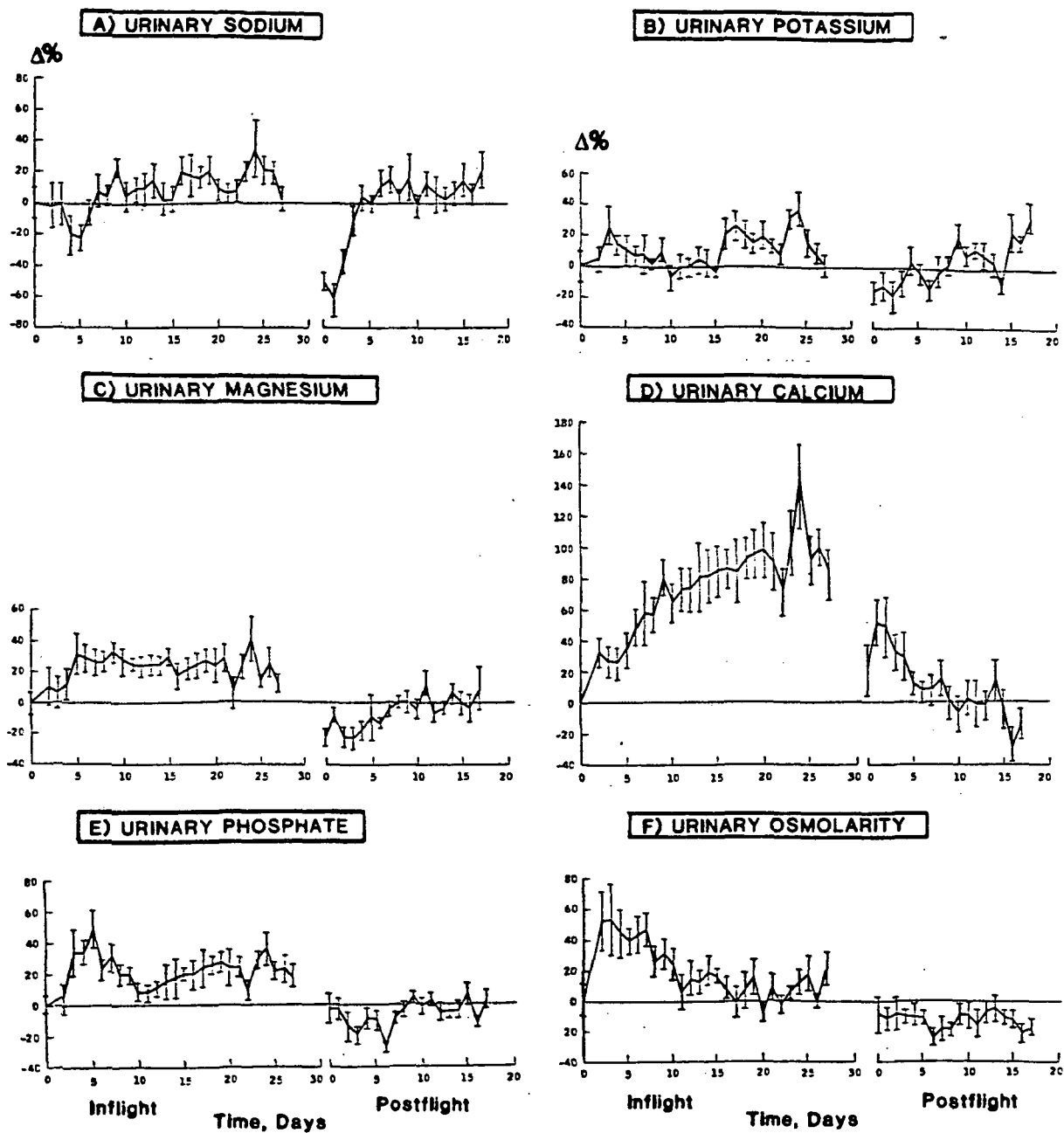


FIGURE 2-5

Daily urinary excretion of electrolytes of Skylab crew during first month inflight and postflight period. Each point represents mean (\pm SE) of nine subjects. Values are expressed as percent change from preflight mean. Data from mission day one is not available.

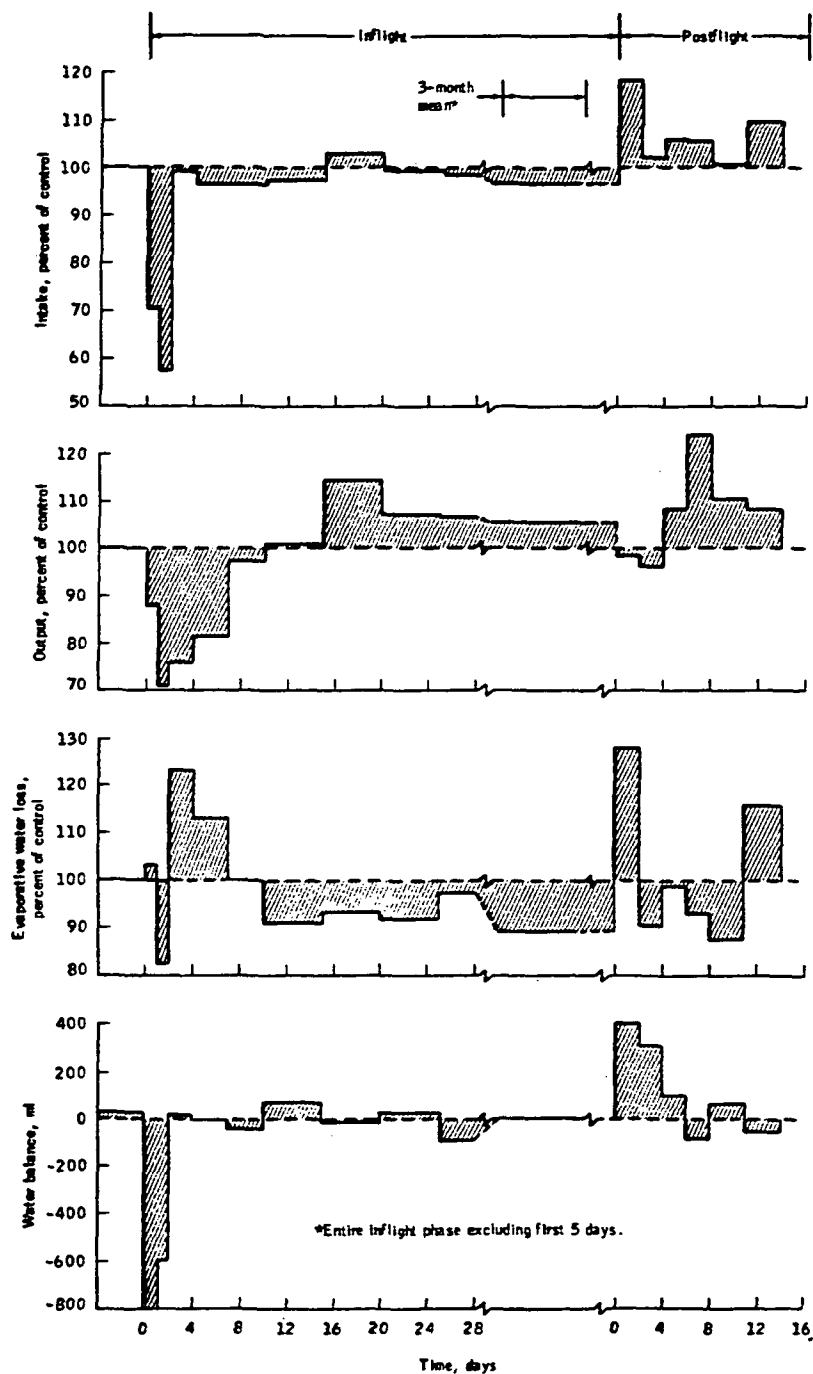


FIGURE 2-6

A composite water balance analysis of the Skylab crew (N=9). Percent changes from control are indicated for the first 28 days and the two weeks postflight. Also shown is the average three month mean that provides insight into long-term changes of intake, excreta and evaporative water loss during a time when the water balance is essentially zero. Intake includes drinking water, water in food and metabolically produced water. Output includes both urine and fecal water. Evaporative water loss was estimated indirectly, (Leonard, 1977).

changes, plasma hormonal responses, urinary parameters, and composite water balance responses of crew-members exposed to 30 days of zero-g. Questions concerning these observations were identified, categorized, and interpreted. These issues formed the basis of a subsequent simulation model analysis, (31) as described below, as well as helping to design the next generation of space-flight experiments.

d) Leonard, J.I. The Behavior of Renal-Regulation Hormones During Hypogravic Stress, TIR 2114-MED-5002. (31)

Homeostatic correction of fluid volume disturbances in zero-g results in reductions of total body water and plasma volume as well as major electrolytes such as sodium. Regulation of these quantities require the participation of renal-thirst mechanisms in general, and hemodynamic, neural, and hormonal controllers in particular. A group of renal regulating hormones, consisting of renin-angiotensin, aldosterone, and anti-diuretic hormone (ADH) have been the focus of many space-flight related studies. An understanding of their role promises to reveal much about the mechanisms which control renal excretion of fluids and electrolytes during exposure to weightlessness. However, the behavior of these hormones has been difficult to interpret or to reconcile with endocrine data obtained from one-g analogs of weightlessness such as, water immersion, head-down tilt, and bed rest. The purpose of this study was to examine these data, describe the major characteristics of the hormone responses, and to assess the controlling mechanisms.

The first section of this report concerns the detailed analysis of one of the hormones, ADH. The second section extends the analysis to include aldosterone and angiotensin, as well as to propose a more generalized theory of renal-endocrine behavior during hypogravic stress. The primary techniques used in this analysis were a series of computer simulations using the modified Guyton model.

The overall conclusion of this study is that each of the renal-regulating hormones appear to repond acutely to volume disturbances and chronically to electrolyte disturbances. During hypogravic maneuvers this leads to an initial suppression of hormone levels and a long-term effect which varies depending on metabolic factors such as diet, sweat loss, physical activity,

and muscle atrophy which can alter the plasma electrolytes. In addition, the simulations reveal that if fluid pressure effects rapidly normalize, a transition phase may exist which leads to a dynamic multi-phasic endocrine response. As indicated in Figure 2-7, these hormones are part of a much larger feedback system that can apparently regulate circulatory extracellular disturbances of various kinds. This diagram illustrates three distinct types of control mechanisms, including hormones, autonomies, and hemodynamics which act to maintain extracellular volume and composition, as well as blood pressure and renal output. Because of these complex and often competing stimulating factors, and the different modes of response, it is difficult to predict the behavior of hormone levels in the plasma or urine, except perhaps by using computer models. Indeed, this may explain why variable findings are often reported for apparently similar bed-rest and head-down tilt studies. Verification of this hypothesis requires the collection of data which have not yet been collected, including measurements of endocrine behavior during the acute phase of space flight and measurement of various circulatory pressures during the longer-term periods of hypogravity. In addition to a knowledge of electrolyte behavior in the body fluids, it is crucial to control such metabolic factors as diet, physical activity, and circadian rhythms.

2.3.2 Erythropoietic Regulation

- a) Leonard, J.I. Systems Analysis of the Erythropoietic Responses to Weightlessness Vol. I.: Mathematical Model Simulations of the Erythropoietic Responses to Weightlessness, TIR 2114-MED-5003. (32)
- b) Leonard, J.I. A Systems Analysis of the Erythropoietic Responses to Weightlessness Vol II.: Description of the Model of Erythropoiesis Regulation, TIR 2114-MED-5004. (33)

Beginning in 1974 and continuing to the present, a systems analysis research program has focused on the hematological problems of space flight. Specifically, it was designed to understand the mechanisms underlying the most significant hematological finding of clinical importance: that is, the reduction in red cell mass. The cornerstone of this analysis was the development and testing of a mathematical model describing the regulation of erythropoiesis. Simulations performed with this model were used to examine the theoretical behavior of erythropoietic regulation so as to provide a means to permit hypotheses to be mathematically tested as a preliminary step in accounting for the "anemia of space flight."

MODEL REGULATION OF EXTRACELLULAR AND CIRCULATORY DISTURBANCES

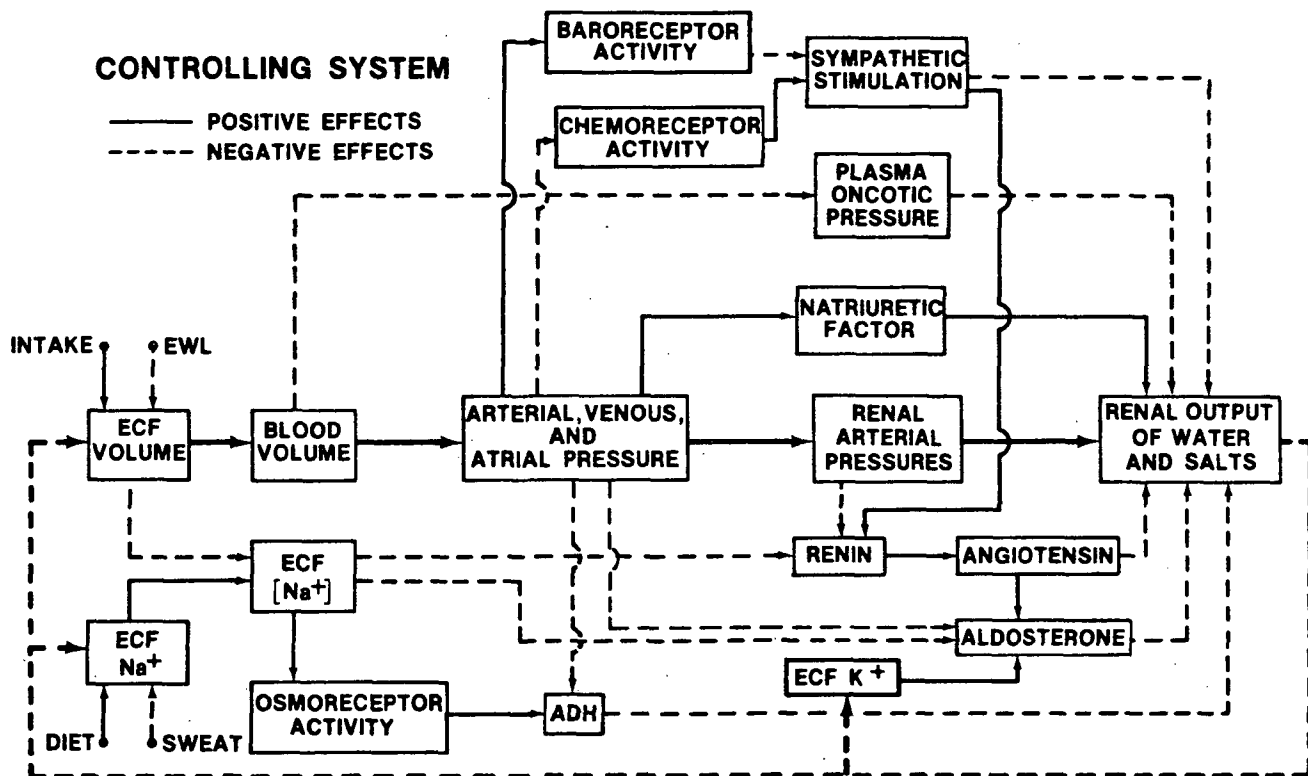


FIGURE 2-7

The first document (32) contains a review of all relevant space-flight data and a set of testable hypotheses which attempt to explain how red cell mass decreases in space flight. The second document (33) describes the details, both mathematical and physiological, of the formulation of the mathematical model used in these studies.

The first document consists of contains several major sections, including a review of previous space-flight findings, the role of tissue oxygenation, and other theoretical considerations of erythropoiesis, hypotheses accounting for the effects of space flight, and a review of the computer simulations of of experimental studies. Part of the study included a valuable collaboration between systems analysts and biological researchers, which permitted testing, in the biological system, hypotheses suggested by the computer model. Results from a number of experimental studies, each characterized by a reduced red cell mass, or suppressed erythropoietic activity, were examined. These included not only space-flight investigations, but also those of bed rest, red cell infusions, dehydration, and descent-from-altitude. The simulation model was valuable in revealing the pathways which were common to all of these situations and provided a quantitative basis for testing whether the same mechanisms were operative in space flight. Figure 2-8 is a representation of the pathways which may be involved in the loss of red cell mass.

The hypothesis most favored in this study is that shifts in plasma volume accompanying hypogravic maneuvers results in an observed mild hemoconcentration which can eventually lead to increased oxygen supply to the renal sensor and cause suppression of erythropoietin and red cell production. The model suggests that red cell mass will stabilize as hematocrits normalize. This process can, therefore, be explained in terms of normal feedback regulation of the erythropoietic system in the face of sustained decreases in plasma volume. Validations of this theory will require, at the very least, confirmation that erythropoietin levels decrease during space flight. Other factors which may have enhanced oxygen delivery shifts in blood flow, P_{50} , and arterial oxygen partial pressure, but no data exist at present concerning these effects. Also, it is believed that inadequate dietary intake or exercise can also suppress red cell mass for reasons that are not well understood. Alternatively, it is possible that an acute increase in red cell

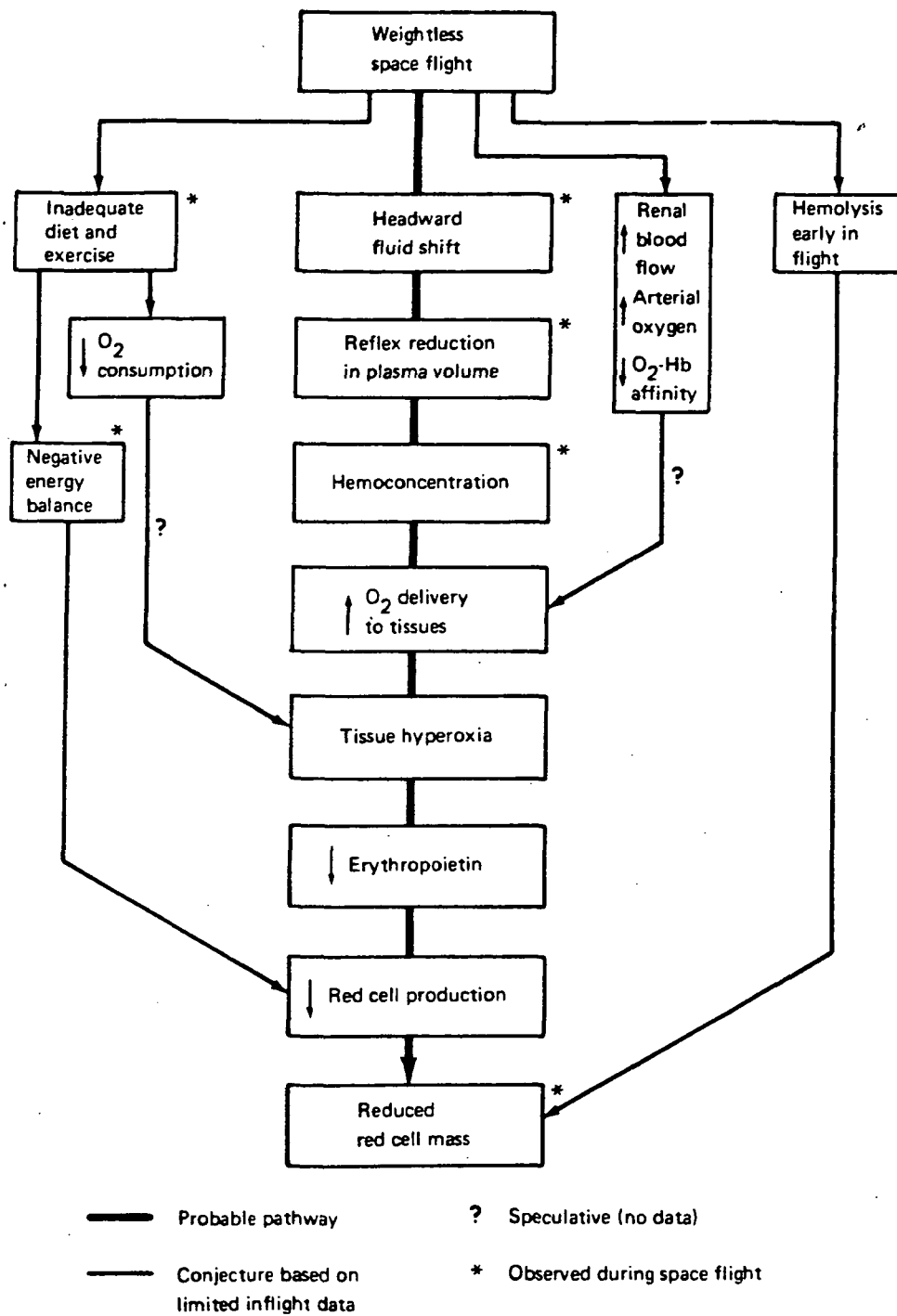


FIGURE 2-8
Pathways which may be involved in the loss of red cell mass during space flight.

destruction could have occurred during flight due to hemorrhage, hemolysis, or sequestration. However, the model suggests that this factor would be contributory to, but not responsible for, the overall zero-g loss of red cell mass.

The concept that red cell mass may be regenerated during space flight, as proposed for the Skylab missions, was examined in detail, and found to be based on misleading assumptions and incomplete interpretation of the data. However, still lacking is a clear understanding of why the three Skylab crews differed in their overall decrements in red cell mass.

For the present, it appears that an answer to the loss of red cell mass will involve an understanding of the basic processes of erythropoiesis, including the role of oxygen transport, as well as the regulation of plasma volume and total blood volume. In order to isolate the basic controlling mechanisms, the subtle changes in energy balance and water balance need to be carefully controlled in future space-flight experiments. Also, an erythropoietin assay with improved resolution is required in order to obtain definitive data regarding this important hormonal regulator.

- c) Nordheim, A.W. A Detailed Analysis of the Erythropoietic Control System in the Human, Squirrel Monkey, Rat and Mouse, TIR 2114-MED-5010. (38)

New experimental studies of body fluid and blood volume regulation during space flight are being considered which utilize, not only human subjects, but animals such as the laboratory mouse, rodent, and squirrel monkey. Mathematical models representing the human and murine erythropoietic systems have been previously developed (21,33) and have been useful in elucidating the mechanisms involved in the control of erythropoiesis and, therefore, blood volume regulation, under a variety of stress situations, including space flight. In order to better understand the erythropoietic system and the previous space-flight results, and to help analyze the data from these new multi-species experiments, a uniform, species-independent, modeling approach to the erythropoiesis system has been developed. This report presents the description of the mathematical formulation of the species-independent model of erythropoiesis regulation, the solutions to the steady-state and dynamic

versions of the model, as well as the individual species-specific models for the human, squirrel monkey, rat, and mouse. The analysis portion of the report is composed of two parts. The first part is a detailed sensitivity analysis of the species-independent model response to parameter changes and how these responses change from species to species. The second part of the study presents an analysis of the species-to-species response of the model to a series of simulated stresses related to the understanding of erythropoietic control systems and the stress of space flight (that is, long-term hypoxic exposure, red cell infusion/loss, infusion of erythropoietin, and plasma volume depletion). Also included in the report as appendices are the derivations of the static and dynamic sensitivity equations.

d) Nordheim, A.W. Use of Modeling in Developing Experimental Protocols Appropriate for Space Flight Experiments. (39)

The development of Life Sciences Experiments for space flight is expensive and the number and frequency of flight opportunities for experiments are limited. For these reasons, it is necessary to maximize the scientific yield of each flight opportunity. This presentation highlighted how modeling can help to maximize the scientific return of flight experiments by helping to analyze existing experimental data, by allowing multiple simulations to be performed, by helping to develop and identify hypotheses, and by providing a means by which alternative hypotheses concerning known or expected space-flight results can be compared. In addition, modeling can be used during the development phase of an experiment; to help design the experiment so that the results will be able to distinguish between competing hypothesis; to help in the allocation of inflight resources in order to achieve the greatest scientific return; and to help design the most appropriate ground-based experimental controls. In those cases where multiple experiments will be conducted in a single space flight, modeling can be used to investigate the impact that other investigations might have on experimental results. This information can be used, if necessary, to redesign the experiments, in order to reduce the inter-experiment interferences. Physiological models have been used in the analysis and design of several previous and pending space-flight investigations. These include models and experiments relating to red blood cell regulation, fluid/electrolyte control, cardiovascular control, and calcium regulation. The presentation included an example of how the model of red

blood cell regulation was used to help design and analyze an experiment flown on the first Spacelab mission. Table 2-2 shows the original blood draw protocol proposed for the Spacelab-One (SL-1) experiments and the final protocol that was used for the mission. The original protocol was revised based upon a series of simulation studies performed by this contractor followed by a reassessment of the blood draw requirements by the SL-1 Principal Investigators. Figure 2-9 shows the results of three simulation studies performed in order to evaluate the impact that the blood draw protocols might have on one of the SL-1 experiments (i.e., INS-103, the erythrokinetics experiment). Table 2-3 presents a comparison of the simulation results for the two blood draw protocol shown in Table 2-2, highlighting the impact that the protocols would have on the expected results of INS-103.

2.4 CONCLUSIONS

Data from the Skylab Life Sciences experiments suggest that there is a tight coupling between the regulation of red cell mass and plasma volume. On these missions, the plasma and red cell losses had opposite trends, with plasma losses getting larger and red cell losses becoming smaller as a function of time in space (17). However, the total decrement, expressed as blood volume loss, appeared to have stabilized after one month; thereafter, the overall blood volume loss was not dependent on zero-g exposure time. These experimental results are summarized in Figure 2-10.

A tentative hypothesis explaining this phenomenon is described below. The set point for blood volume regulation is reduced in weightlessness because of the tendency for central circulatory volume overload. Plasma volume losses are achieved by complex renal-thirst mechanisms (see Figure 2-1), while suppression of erythropoiesis occurs due to changes in tissue oxygen demands brought about by changes in the characteristics of the circulating blood (hematocrit, oxygen carrying capacity, etc.), altered bone marrow function, or a combination of both factors (see Figure 2-8). In addition, it can be postulated that acute plasma volume decrements lead eventually to a normal proportional reduction in red cell mass; however, secondary adjustments in plasma volume occur (due possibly to the decreased red cell mass and may be in

TABLE 2-2

COMPARISON OF BLOOD DRAW PROTOCOLS

SL-1 Blood-Draw Protocol

	<u>Day</u>	<u>Original Protocol Blood Volume (ml)</u>	<u>Final Protocol Blood Volume (ml)</u>
PREFLIGHT	F-30	127	69
	F-15	123	
	F-11		60.5
	F-1	123	60.5
INFLIGHT	MD-2	48	40.0
	MD-4	32	25.0
	MD-6	71	
	MD-8		48.0
POSTFLIGHT	L+0	127	69.0
	L+1	80	50.5
	L+7	114	60.5
	L+14	84	59.0
		<hr/> 929 ml	<hr/> 542 ml

EXPERIMENTSEXPERIMENT TOTALS

INS 103 - ERYTHROKINETICS
 INS 105 - IMMUNE RESPONSE
 IES 032 - ENDOCRINOLOGY
 MEDICAL OPERATIONS

78.0
 64.0
 250.0
 50.0

 542.0 ml

SIMULATION RESULTS FROM 1) ZERO-G STRESS ONLY (---),
 2) SL-1 BLOOD DRAW PROTOCOL ONLY (---), AND 3)
 COMBINED ZERO-G STRESS AND SL-1 BLOOD DRAW PROTOCOL
 (—).

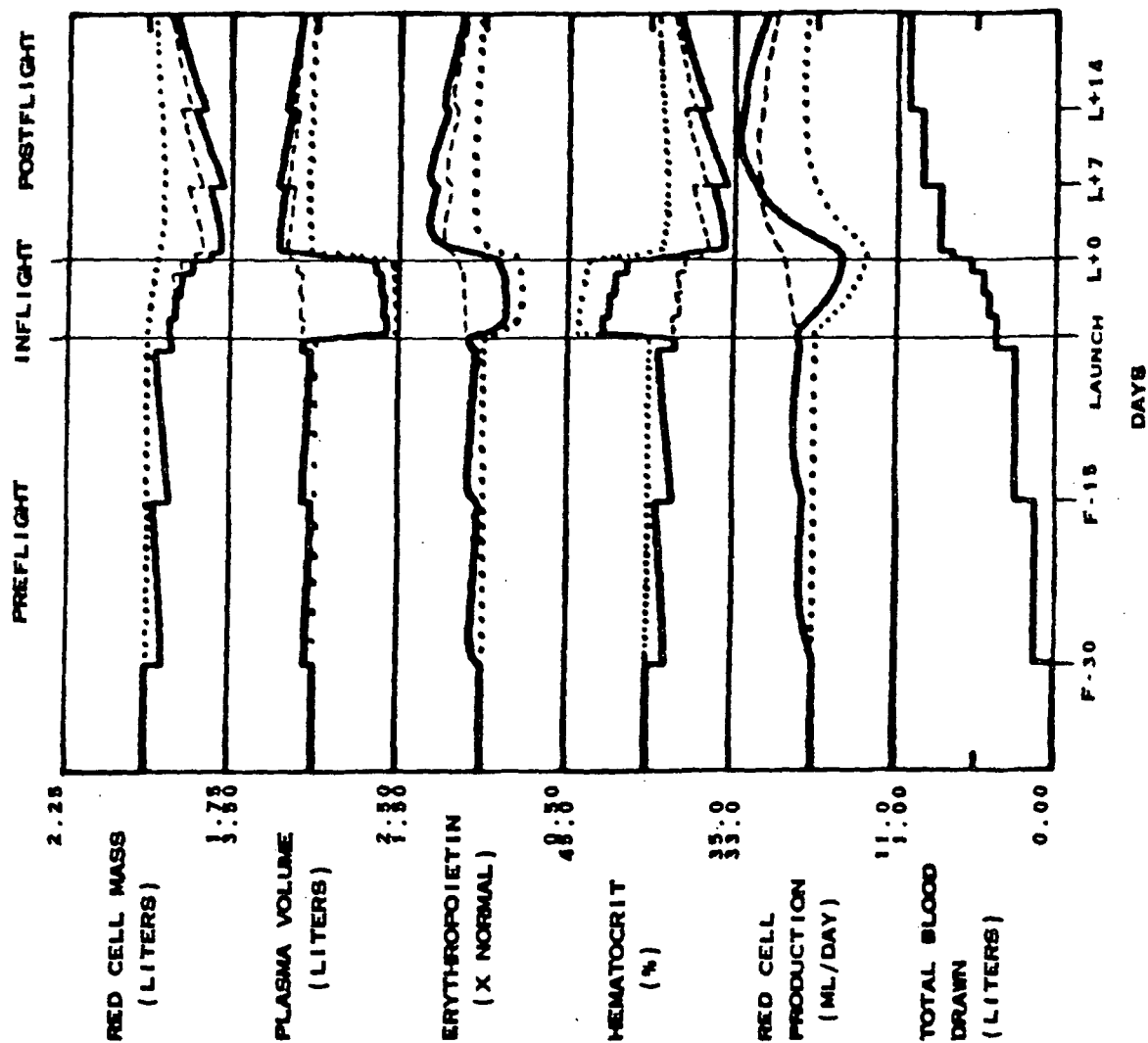


FIGURE 2-9

TABLE 2-3

COMPARISON OF RESULTS FROM THE TWO DIFFERENT BLOOD DRAW PROTOCOLS

Results of the Computer Simulation of the SL-1 Blood Draw
Protocol for MD6/MD8 and L+1. Results as % Δ Preflight.

<u>MD6/MD8 Values</u>	<u>Original Protocol</u>		<u>Final Protocol</u>	
	With Blood Draws	Without Blood Draws	With Blood Draws	Without Blood Draws
Hematocrit	+ 8.2	+ 11	+ 7.4	9.0
Erythropoietin	- 14.0	- 21.4	- 16.0	- 21.0
Red Cell Mass	- 4.5	- 1.0	- 3.7	- 2.0
Red Cell Production	- 19.3	- 28.4	- 24.0	- 31.0
 <u>L+1 Values</u>				
Hematocrit	- 6.0	- 1.1	- 4.6	- 1.0
Erythropoietin	+ 2.2	- 10.1	0.0	- 10.0
Red Cell Mass	- 8.8	- 1.6	- 6.7	- 2.0
Red Cell Production	- 18.7	- 30.8	- 23.1	- 32.0

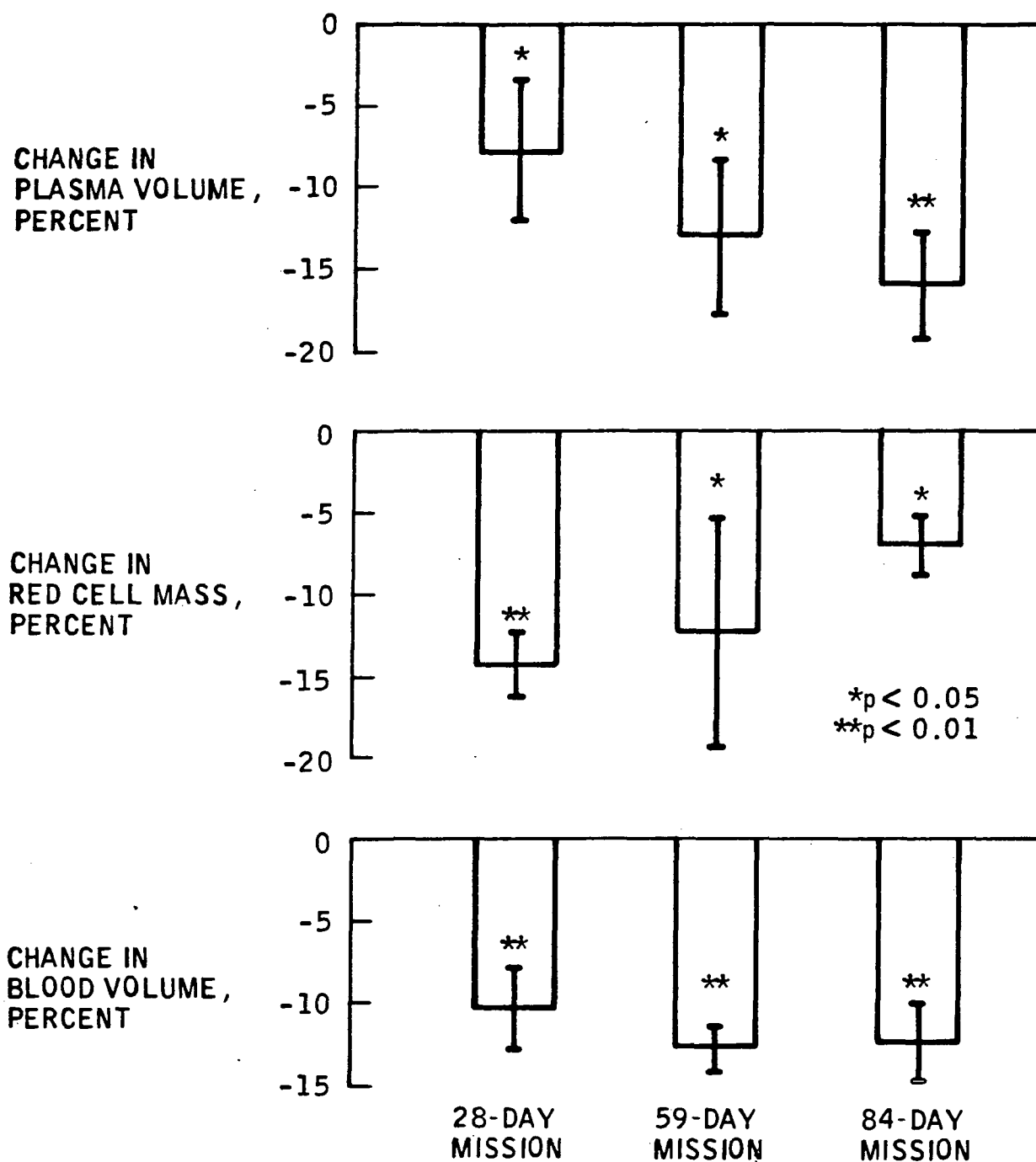


FIGURE 2-10

Changes in plasma volume, red cell mass, and total blood volume of the Skylab crew. Each bar represents the mean (\pm SD) difference between preflight and postflight measurements for each three-man mission. The postflight value was obtained on the day of recovery.

a direction opposite to the initial plasma volume due to the headward fluid shift), so that the total blood volume loss is constant.

FUTURE PLANS

Based upon the work performed under the current contract, the contractor has identified several areas of work that still need to be completed with respect to developing/testing the hypotheses concerning overall blood volume regulation during zero-g exposure. The major areas of work that still need to be addressed have to do with the analysis of recent space experiments relevant to the issue of blood volume regulation (i.e., the SL-1 experiments), analysis of the results from the upcoming SLS-1 fluid regulation experiments, as well as the development of a new generation of experiments specifically designed to test some of the most promising fluid regulation hypotheses (see the discussion of Task 3 "Design of Key Experiments Related to Body Fluid and Blood Volume Regulation" in Section 5.0 of this report). The results of these experiments are expected to provide a wealth of information.

Inherent to evaluating the result of the SL-1 experiments and any other upcoming space-flight experiment related to blood volume regulation, is the question "what impact do the experimental protocols, to be used during these experiments, have on the actual physiological systems being measured?" In particular, the effects of tracer injections and blood draws (both frequency and volume of blood draws pre, in, and postflight) need to be evaluated, as well as the effects of other experimental and non-experimental activities or restriction such as exercise levels and durations, dietary and fluid intakes, and any possible drug interactions. While it is beyond the scope of the stand-alone Guyton model to study all of these possible factors, several of these effects can be studied using this model or other models developed by this contractor (38). Preflight, the models can be used in order to evaluate possible interferences and either help change the proposed protocols (for those experiments in which this contractor has played a role in developing), or the models can be used in order to help define the most appropriate ground-based controls for the inflight experiments. Postflight, the models can be used to help differentiate between true space-flight results and those results that are due to other causes.

In summary, the majority of the future work that has been identified with respect to blood volume regulation centers around the analysis and interpretation of new space-flight data that has been, or will be, collected on upcoming Shuttle missions; and the development and follow-up analyses of a new generation of space-flight experiments designed to address the blood volume regulation issues described in the main body of this report.

3.0 ORTHOSTATIC INTOLERANCE AND CARDIOVASCULAR DECONDITIONING

There are two tasks in this area of physiological concern as delineated in the Statement of Work (see Appendix A):

Task 4 - Physiological and Modeling Analysis of Cardiovascular Deconditioning and Orthostatic Intolerance

Task 5 - Modeling Analysis of Countermeasures for Orthostatic Intolerance

A total of five technical reports (25,35,41,42,43) were prepared on the above task areas during the contract period. The work performed is detailed in these reports and is summarized below.

3.1 INTRODUCTION

A well-documented effect of a stay in the microgravity environment of space is a decrement in the amount of total circulating blood volume. The loss of blood volume appears to be the predominant factor responsible for the reduction in orthostatic tolerance* observed following exposure to weightlessness or related one-g conditions such as bed rest. The decrease in orthostatic tolerance is a problem of operational concern in Shuttle flights because of the fact that during reentry maneuvers, the crew are exposed to headward accelerations ($+G_z$) larger than one-g in magnitude. The combination of such high headward g-forces and the loss blood volume can exert a powerful influence upon cardiovascular function. In particular, circulatory pressures and flows to the cerebral region may be reduced to such critical levels as to seriously impact crew performance at a time when performance decrements can be least accommodated.

There are two putative countermeasures that are used to improve the g-tolerance of the Shuttle crewmembers during reentry. These are: (i) pre-reentry

* Factors other than decreased blood volume may be involved in the orthostatic intolerance of zero-g. These include decreased cardiac contractility and degraded baroreceptor responsiveness. However, no definitive findings regarding their involvement have been made. In this report, we will consider only blood volume as a causative factor.

replacement of fluids and electrolytes or fluid-loading, and (ii) application of lower body positive pressure with the aid of an anti-g garment. The beneficial effects of these two remedial measures have long been known. However, the details of the physiological responses resulting from their use have not been fully evaluated. Such an evaluation would require data over a range of parameters of the countermeasures; i.e., volume and composition in the case of fluid-load and inflation pressure in the case of anti-g suit. It is not feasible to obtain the requisite data experimentally in an operationally oriented environment.

3.2 APPROACH

One possible approach to study orthostatic intolerance and the effects of fluid-loading and anti-g suit as countermeasures is to use computer simulations of mathematical models. Such an approach was employed to provide theoretical answers to operational questions related to Shuttle reentry. Two different mathematical models of the circulatory system were used. One is the Guyton model describing the long-term circulatory, fluid, and electrolyte regulation (13). It was used to study the effects of pre-reentry replacement of fluids and electrolytes. The basic model consisting of five vascular compartments connected to an interstitial fluid compartment and a cellular fluid compartment was modified to include leg vascular and tissue compartments and gravity-dependent elements (27). The modified model has been used to simulate water immersion (23) and head-down tilt (26), as well as to analyze fluid-electrolyte alterations in weightlessness (24).

The second model is a short-term model of the cardiovascular system based on the assumption of a closed vascular system with no provision for fluid filtration into the extravascular space. The systemic circulation and the heart are represented by a number of compartments in the model. The equations relate the pressures and flows through lumped parameters such as resistance and compliance of the vascular compartments. It is a beat-to-beat model valid for simulation of events lasting less than 30 minutes. It has been used successfully to simulate responses to exercise, lower body negative pressure (LBNP) and tilt tests under one-g conditions (6). More recently, it has been utilized both to reproduce tolerance to centrifugation (41) and to predict cardiovascular responses during STS reentry (25), as summarized in Section

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3.3.2 Cardiovascular Response During Shuttle Reentry

A theoretical study was undertaken soon after the first STS flight to evaluate the factors that contribute to orthostatic intolerance during and following reentry and to predict the likelihood of impaired crew performance. The findings of this computer simulation study were presented at scientific meetings (22,42), but the details had not been reported. Two reports (25,41) describing the various simulations performed (using the pulsatile cardiovascular model) were prepared and released during this contract period.

The reports include studies on validation of the pulsatile cardiovascular model for g-stress, studies on the effects of blood volume loss, simulations of cardiovascular response during STS-1 reentry and crew postflight stand tests, and predicted response of STS-2 reentry. The validation studies involving g-tolerance indicated the need for the presence of intact autonomic reflexes even at low levels of g-stress. This implied that with degraded baroreceptor responsiveness following weightless exposure, which was not assumed in the simulation studies (footnote on page 31), a further reduction in orthostatic tolerance during reentry could result beyond that due to a loss of blood volume alone. The results from studies on the effects of blood volume loss showed that reentry g-forces with peaks less than 2 G would be very well tolerated with a normal blood volume (Figure 3-1). However, these same g-stresses, when accompanied by only moderate blood volume losses, comparable to those that occur in space flight, might be reason for medical concern. Furthermore, some type of impairment would become more likely, if blood volume losses were severe, or if aspects of cardiovascular deconditioning other than blood volume loss were present. The results were in agreement with conclusions from early ground-based experiments, as well as from observations of early STS flights.

3.3.3 Countermeasures for Orthostatic Intolerance (Task 5)

Fluid-loading: The influence of fluid-loading upon the time-course of changes in cardiovascular parameters during reentry was studied with the aid of the Guyton model of the circulatory system. Weightless conditions were simulated by placing the model in a head-down tilt position of -6° . The STS-1 reentry g-profile with a peak g-force of approximately 1.5 G (typical of most STS

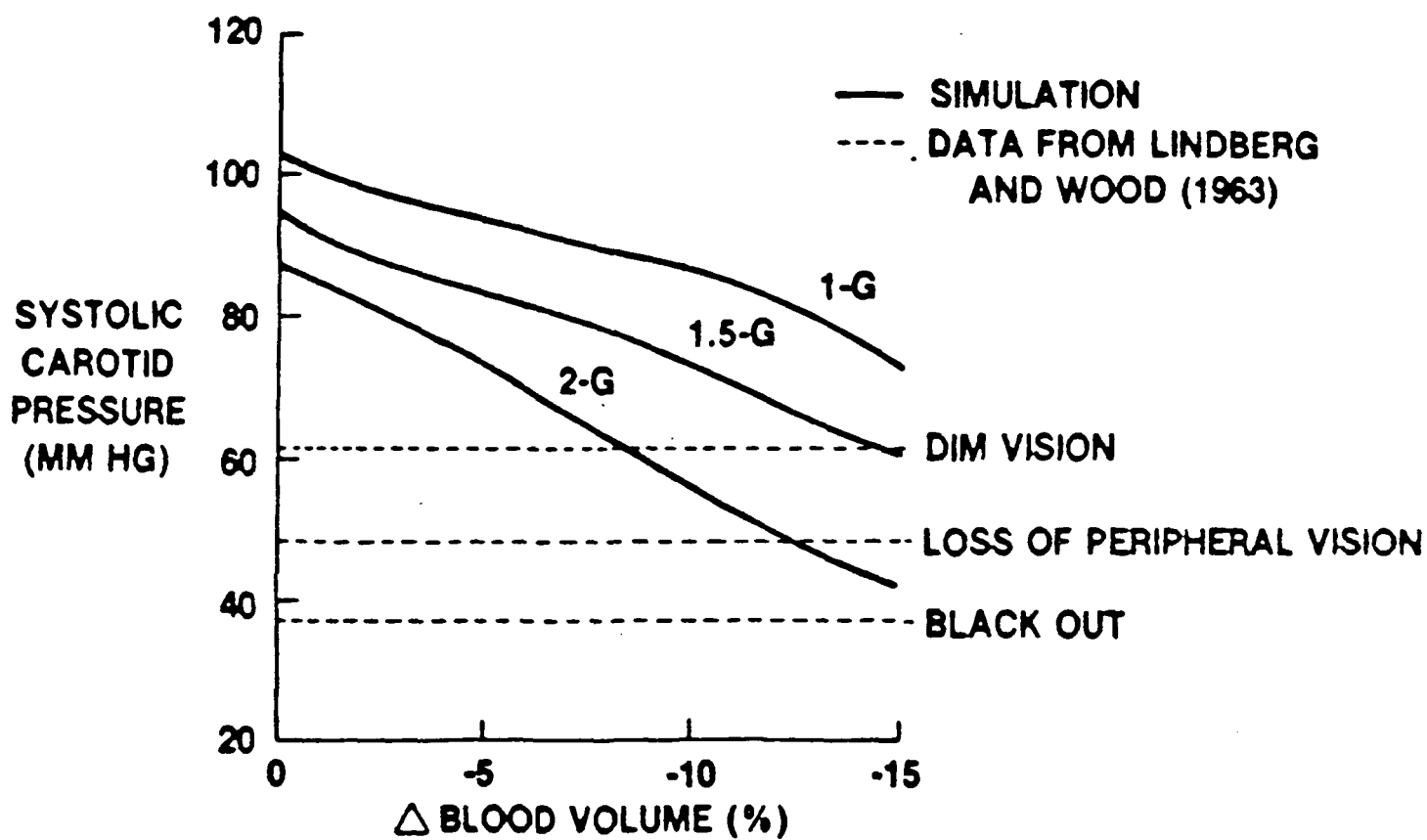


FIGURE 3-1.

Effect of acceleration stress and altered blood volume on vision

flights) was used to simulate reentry g-stress. The time of ingestion prior to reentry and the salt concentration of the fluid-load were varied, while keeping its volume constant (one liter in all simulation runs). It was not necessary to vary the volume to understand the general behavior of the fluid-load as this has the effect of only amplifying or attenuating the elicited changes in physiological parameters.

The simulation results showed that the time of ingestion was not critical for fluid-loads in which salt content was very low. Judging from the time course of return of the cardiovascular parameters to preflight baseline levels, a hypertonic fluid-load administered just prior to reentry had the maximum beneficial effect in improving the orthostatic tolerance during and following reentry (Figure 3-2). In most instances, the time-course of changes for different salt concentrations were similar. Since the loss of fluids is not the only causative factor behind space flight-induced cardiovascular deconditioning compensation for fluid loss alone cannot be expected to reverse completely the adaptive manifestations of weightless exposure.

It was plausible that the effectiveness of the fluid-load could be enhanced by lessening the excretion of the ingested fluid. Indeed, this was found to be true with the addition of an anti-diuretic agent to the fluid-load. In this case, the plasma volume increase obtained at the end of the reentry period was approximately 140 ml higher than for the corresponding situation without the addition of an anti-diuretic agent, assuming that the action of the agent was total, immediate, and present for the entire duration of reentry (best-case scenario).

Anti-g Suit: The pulsatile cardiovascular model was utilized to demonstrate the effects of applying lower body positive pressure (anti-g suit inflation) in order to improve g-tolerance in the face of a diminished blood volume. Simulations were performed by varying the anti-g suit inflation pressure during exposure to a sustained g-force of 2 G. The results clearly pointed to the nonlinear nature of the cardiovascular system behavior (Figure 3-3). There was a linear change in cardiovascular parameters with increase of suit pressure up to 40 mmHg. Thereafter, the response exhibited a greater sensitivity to suit pressure. Based on the computed systolic carotid pressure levels, the minimum suit pressure required to avoid vision impairment

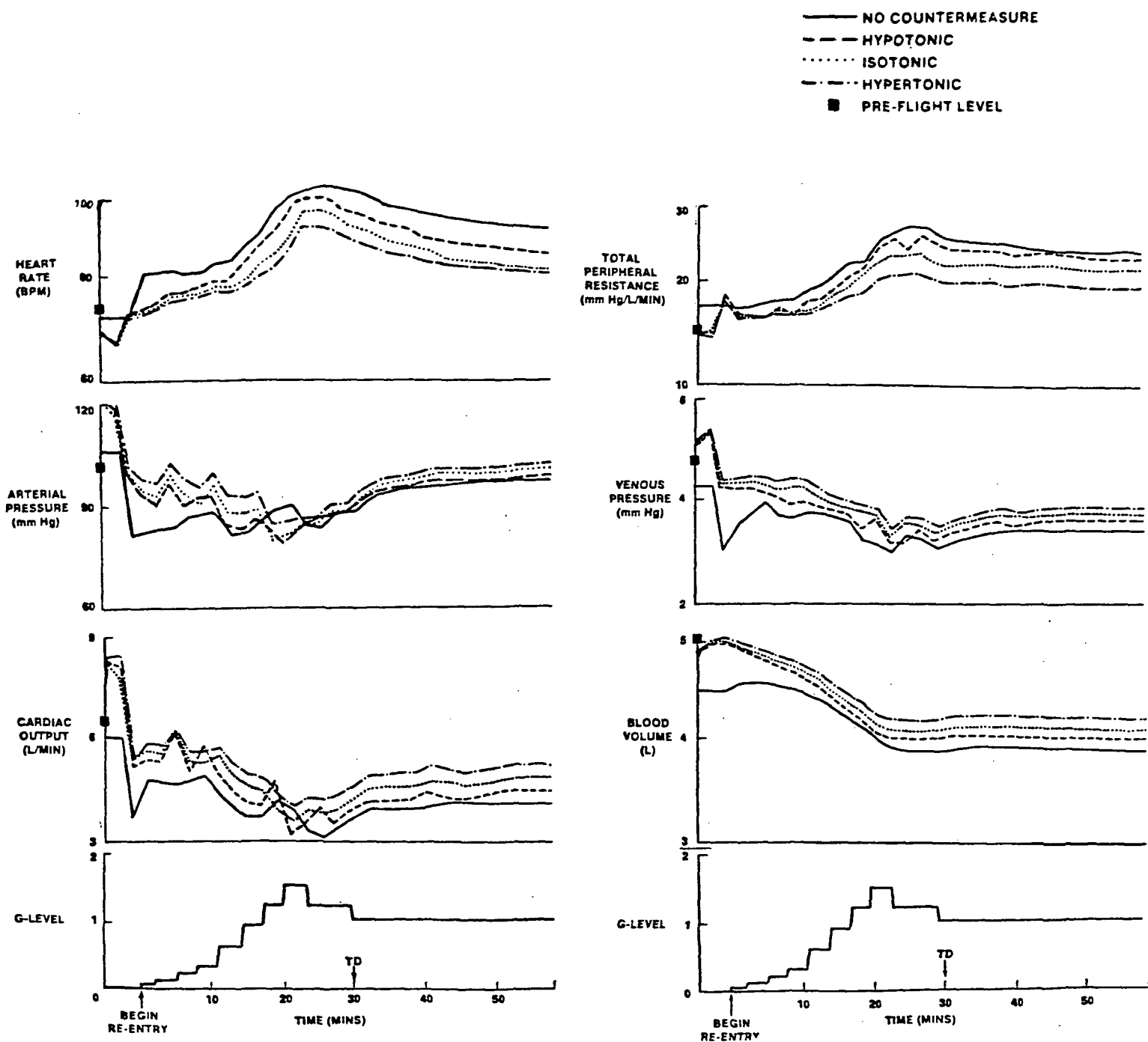


FIGURE 3-2.

Effect of varying the salt concentration of the fluid-load on cardiovascular response during reentry. Ingestion time is just prior to reentry.

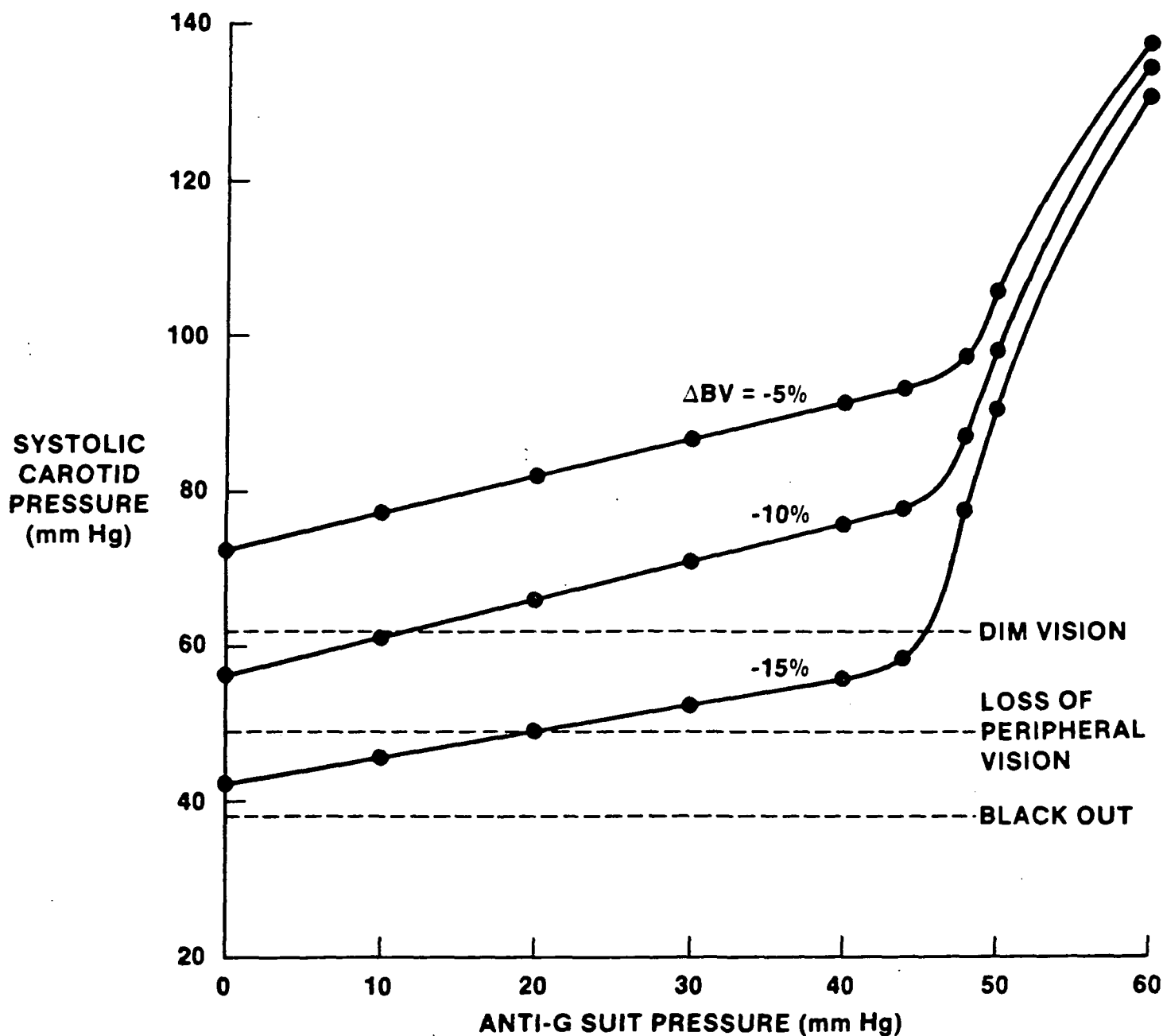


FIGURE 3-3

Effect of Anti-g suit inflation during 2-g acceleration. The simulated data are shown in solid lines. The threshold levels for visual symptoms shown in broken lines are from Lindberg and Wood

increased with the magnitude of blood volume reduction, as one would expect. The simulation results indicated that, for g-forces of 2 G and less, the use of an anti-g garment would be warranted only if the blood volume loss exceeded 10 percent.

3.4 CONCLUSIONS

The loss of fluids is not the only causative factor underlying space flight-induced cardiovascular deconditioning. Some of the other possible mechanisms involved include increase peripheral resistance, changes in cardiac contractility, significant pressure/flow and compliance changes in the lower extremities.

Blood volume loss plays a key role in the development of cardiovascular deconditioning and the accompanying orthostatic intolerance during space flight. Depending on the severity of loss, the reentry acceleration stress may be detrimental to physiologic function and may place the physiologic status of the crew near the borderline of some type of impairment.

With regard to countermeasures for orthostatic intolerance, fluid-loading is the simplest of all from an operational standpoint. Ingestion two hours prior to reentry would yield optimal results with minimal operational inconvenience. Increasing the salt content of the fluid-load would enhance the beneficial effects. Further enhancements may be achieved by the addition of an anti-diuretic agent to the fluid-load so as to retard rapid excretion of the ingested fluid. In the case of lower body positive pressure as a countermeasure, the simulation results indicate a minimal pressure of approximately 50 mmHg would provide adequate protection against vision impairment with g-forces up to 2 G and blood volume losses up to 15 percent.

Finally, the studies demonstrate the usefulness of modeling and simulation in addressing questions of operational interest. Future studies should include 'testing' of new countermeasure combinations as they are being suggested.

4.0 CALCIUM REGULATION AND BONE ATROPHY

There is one task in this area of physiological concern as delineated in the Statement of Work (see Appendix A):

Task 7 - Completion of Expanded Calcium Model and Data Base

4.1 INTRODUCTION

A mathematical model of the calcium metabolic system was developed on two previous contracts (10,11) for the purpose of contributing to theoretical analyses and development and testing of hypotheses related to calcium metabolic changes which have been observed in human subjects during exposure to hypogravic environments. Specifically, the model has been used to define regulatory and interactive calcium metabolic events that may be occurring within the normal, healthy physiological system during an applied experimental stress. In this case, the applied experimental stress is a reduction in the gravitational load to the skeletal system due to zero-g exposure.

The calcium model is a compartmental, feedback control system that utilizes ordinary differential equations to relate passive calcium fluxes between the major pools of the calcium metabolic system and the external environment; specifically, the extracellular fluid, intestinal, renal, and skeletal system (Figure 4-1). Three hormonal subsystems, parathyroid hormone, Vitamin D, and calcitonin, actively stimulate or inhibit, via feedback control, the passive calcium fluxes. Originally, the model was developed by Jaros, Coleman, and Guyton (15). It was transcribed from the published report, and implemented on a Digital Equipment Corporation VAX 11/780 (2,11).

The model has been validated with experimental bed-rest and space-flight data and has contributed to hypotheses testing and suggesting physiological events that may be occurring within the system (3). However, one of the main systems of investigative interest in the area of hypogravic calcium metabolic research is the skeletal system. Unfortunately, the main disadvantage of the model described above is the lack of physiological representation and specificity within the skeletal system. The model contains only a single subsystem

MAJOR COMPARTMENTS AND FLUXES OF THE CALCIUM MODEL

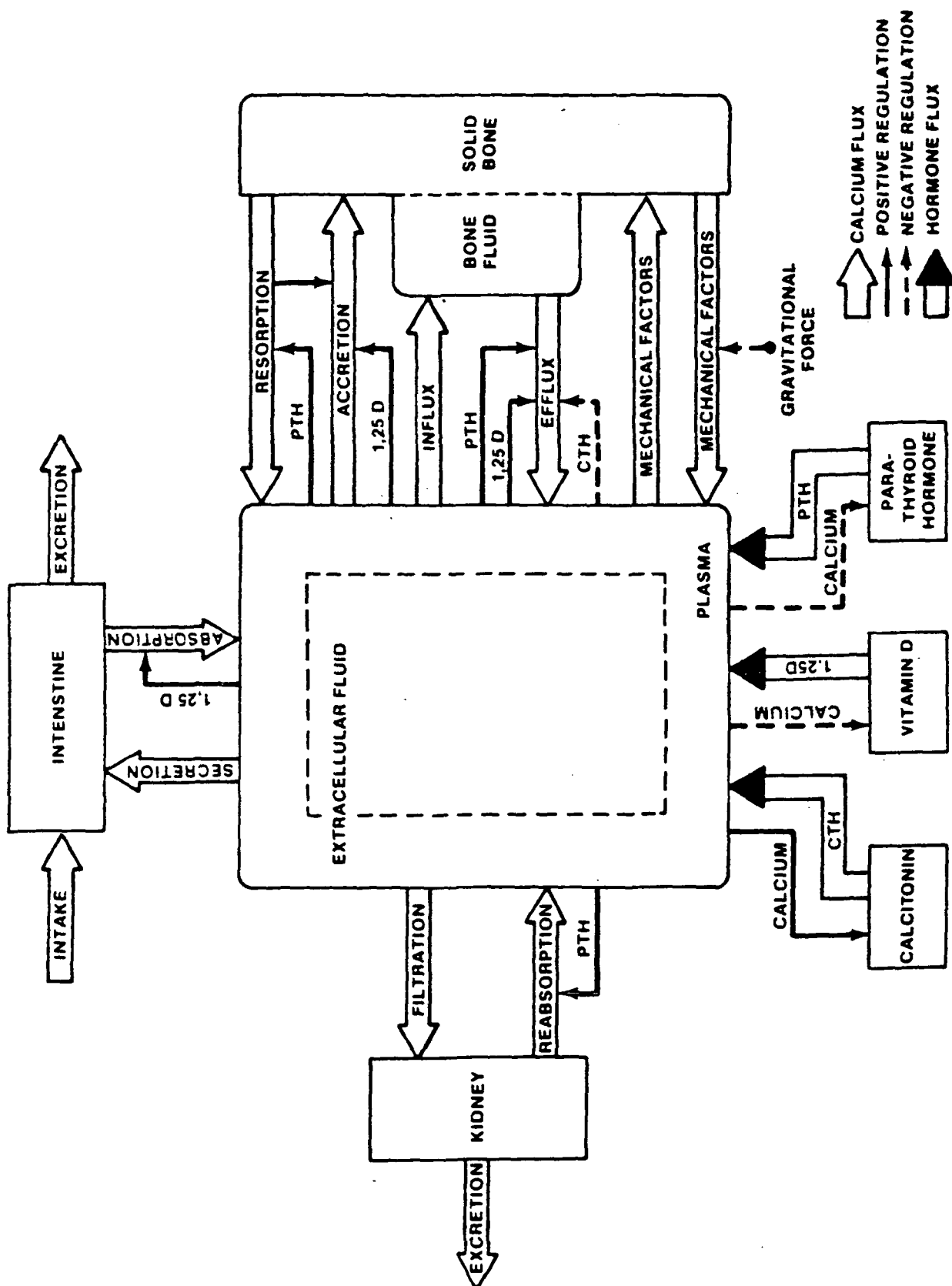


FIGURE 4-1

representation of the skeletal system whose mathematical equations represent gross estimates of the rates of calcium efflux and influx between bone, bone fluid, and extracellular fluid compartments. As a result, the model is, and has been, useful in developing and testing hypotheses of soft tissue changes during hypogravic exposure, but is more limited for testing hard tissue changes.

Jaros, Guyton, and Coleman (16) later published a report which expanded the single skeletal subsystem representation of the calcium model into a series of eight, physiologically representative, subsystems. In addition, the report contained information leading to the inclusion of a phosphorus subsystem. The addition of a phosphorus subsystem is highly desirable since reports of bed-rest studies conducted at the U.S. Public Health Hospital in San Francisco have suggested that supplementation of dietary phosphorus is an effective countermeasure to the urine calcium losses recorded during bed rest and space flight. Consequently, the skeletal and phosphorus subsystems were transcribed and incorporated into the calcium model (2) during the previous contract period (Figure 4-2).

Development and implementation of the expanded model during the previous contract period did not result in a fully operational program. The model was operational in the steady-state, but execution failed during simulations with applied as experimental stresses. The expanded calcium model exhibited instabilities which generally resulted in one or more variables exceeding the output limitations. This prevented execution of the program. The main objective of the present contract in the calcium metabolic discipline has been to correct the instabilities during execution of the expanded calcium model and to deliver to the customer, a model that is fully operational and applicable to the study of calcium metabolic changes during exposure to hypogravic environments.

4.2 APPROACH

Although the Statement of Work contains only one task in the calcium metabolic discipline, the scope of work completed includes three subtasks. These are: (i) to determine, and develop a technique to remove, the exact source of the

The diagram illustrates the endocrine system's components and their interactions. The central 'PLASMA' box is connected to several other boxes: 'INTESTINE', 'KIDNEY', 'BONE FLUID', 'SOFT TISSUE', and 'SOLID BONE'. The 'INTESTINE' box has arrows for 'EATCAL' and 'EATPHO' entering, and 'FECCAL' and 'FECPHO' exiting. It also has arrows for 'ALIPHO', 'ALICAL', 'CIN', 'SECPHO', and 'SECCAL' entering the 'PLASMA'. The 'KIDNEY' box has arrows for 'PTH', 'CA', 'GEPH', and 'REABPH' entering, and 'EXCAL' and 'EXPHO' exiting. The 'BONE FLUID' box has arrows for 'PTH', 'CIN', 'CTH', 'RESOCAL', and 'PTH' entering, and 'OCYICA', 'OCVPI', 'CABUE', 'ASSICA', 'ASSPI', 'ACRET', and 'ACRETP' exiting. The 'SOFT TISSUE' box has arrows for 'PTH', 'CIN', 'CTH', 'RESOCAL', and 'PTH' entering, and 'PIDT' and 'CA' exiting. The 'SOLID BONE' box has arrows for 'PTH', 'CIN', 'CTH', 'RESOCAL', and 'PTH' entering, and 'OCYICA', 'OCVPI', 'CABUE', 'ASSICA', 'ASSPI', 'ACRET', and 'ACRETP' exiting. The 'PLASMA' box has arrows for 'PTH', 'CIN', 'CTH', 'RESOCAL', and 'PTH' entering, and 'OCYICA', 'OCVPI', 'CABUE', 'ASSICA', 'ASSPI', 'ACRET', and 'ACRETP' exiting. The 'PLASMA' box also has arrows for 'VITAMIN D', 'VITAMIN B12', and 'CALCITONIN' entering, and 'PARA-THYROID HORMONE' exiting.

43

numerical instabilities that occur in the expanded calcium model during simulations; (ii) to validate the operational model with data from the bed-rest studies conducted at the U.S. Public Health Hospital in San Francisco; and (iii) to analyze the impact of using dietary supplements of phosphorus and calcium as countermeasures for demineralization during bed rest. These topics are discussed below.

4.3 RESULTS

a) Development of an operational expanded calcium model

During this contract period, extensive debugging and programming were done on the expanded calcium model. Efforts were made to isolate and identify the source of the instabilities early in the contract period. Three of the skeletal subsystems whose interactions produced a positive feedback effect were isolated as the source of the instabilities. The positive feedback effect was eliminated by introducing damping factors into the program. This correction resulted in a model that could run to completion, but, unfortunately, developed instabilities even in the steady-state. Ultimately, operational stability was achieved by restructuring the model as explained in the following paragraphs.

During the previous contract period, when the model was initially implemented on the computer, the subsystems were transcribed directly from the report of Jaros, Guyton, and Coleman (15). In this format, the number of parameters contained in the data base and common block exceeded the maximum number of parameters that the main program could read and store (in excess of 300 parameters). In order to solve this problem, most of the subsystem constants were deleted from the data base and common block and were inserted into the appropriate subsystems to be read as internal constants. This format resulted in a program that was executable and easy to compare with published diagrams of the model, but difficult to debug.

As a further attempt to reduce the number of parameters and the number of calculations of the model, all eighteen of the model subsystems were streamlined by combining equations where possible and by replacing selected

constants with their numerical value. Operationally, the run time of the model improved and the magnitude of the instabilities decreased; however, they were not eliminated.

Reducing the magnitude of the instabilities provided the opportunity to identify the source of the remaining problems within the model such as round-off errors on critical regulatory variables. This was corrected by defining negligible round-off values as those values ± 0.00001 from the baseline value of the given variable. With these modifications, the instabilities were eliminated from the model output and the model has become fully operational. The modifications and corrections to the expanded calcium model are recorded in an addendum to the user's guide (4).

b) Model Validation

Once the expanded calcium model became fully operational, the next step was to validate the model through assessment of the degree of correspondence between model output and actual experimental data by comparison of the qualitative and quantitative trends of common variables. The objective of this type of analysis is to demonstrate the ability of the model to reliably simulate selected responses of the calcium metabolic system to given experimental stresses and, thereby, gain confidence in the use of the model. During this contract period the expanded calcium model was tested for a variety of simulation results.

The first simulations compared model output with the published simulation results of Jaros, Guyton, and Coleman (16). The purpose of these validation tests was to ensure that the expanded calcium model retained the basic characteristics of the published model from which it was derived.

Following the success of the above validation tests, simulations of calcium metabolic changes which occur during bed rest were executed on the expanded calcium model. These results were compared to the results of the bed rest studies conducted at the U.S. Public Health Hospital in San Francisco (40) and presented in a report by Brand (5). In addition, they were compared with results obtained using on the original calcium model (3).

The initializing assumptions for the above simulations were the same as those for simulations conducted on the original calcium model (3). The volume of extracellular fluid was decreased by one liter and calcium was forced out of the bone through the manipulation of one or more skeletal variables. In the original model the initializing loss of calcium from the skeletal was generated through the reduction of a gravitational term. In the expanded model, because of the improved physiological representation, several initializing skeletal factors were examined. The bed-rest simulations were initialized first, by decreasing the rate of bone accretion; second, by increasing the rate of bone resorption; and third, by doing both simultaneously.

Qualitatively, simulations initialized with any of these three initializing options generated results similar to those of the experimental bed-rest studies and of the bed-rest simulations with the original calcium model. The effective decrease in skeletal calcium causes the plasma calcium concentration to increase. As the plasma is filtered by the renal system much of the excess calcium is passively eliminated and the system begins to return to a steady homeostatic state. In the expanded model, however, homeostasis is not achieved because the renal system is unable to compensate completely for the consistent loss of calcium from the bone. Ultimately, this results in a plasma calcium concentration that remains above the baseline value (from 5 to 9 percent) and a calcium balance that becomes increasingly negative. Within two to three weeks of simulation time, the production rate of 1,25-dihydroxy-vitamin D (1,25-(OH)₂D) decreases which, in turn, results in a long-term inhibition of the intestinal calcium absorption rate. With the decrease in intestinal calcium input, the plasma calcium concentration begins to fall. Once again, the calcium metabolic system appears to approach a homeostatic state, but with a continual, daily loss of whole-body calcium.

Quantitative comparisons of selected maximum values derived from the simulation and experimental data are presented in Table 4-1. The intestinal calcium absorption rates and plasma 1,25(OH)₂D concentrations are comparable to, while the urine calcium excretion rates are significantly below, the experimental values. Due to the variability of the experimental PTH data (5), the PTH simulation data are difficult to assess.

TABLE 4-1

Results of Experimental And Simulated Studies of Calcium Metabolism
During Bed Rest (percent change from baseline)

	<u>Urine</u> <u>Excretion</u>	<u>Plasma</u> <u>Calcium</u>	<u>Intestinal</u> <u>Absorption</u>	<u>Plasma</u> <u>PTH</u>	<u>Plasma</u> <u>1,25(OH)2D</u>
Simulation					
Expanded Model	+ 10	+ 9	- 10	+ 61	- 13
Original Model	+ 45	+ 4	- 13	- 30	- 12
Experimental	+ 45	0	- 18	+317	- 23

In conclusion, the simulation results demonstrate the potential of the model to be used as a theoretical tool for analyzing calcium metabolic data obtained from hypogravic studies. Based upon our previous experience with modeling and simulation studies, we believe that the model will also be useful as a theoretical tool for hypothesis testing. An example of this type of use of the model can be demonstrated by analyzing why the calcium metabolic system is not dramatically affected by the nature of the skeletal initialization. In this particular case the model is structured such that the bone acts as a buffer to the calcium concentrations in the extracellular fluid. Regardless of whether calcium is prevented from being deposited into, or is eliminated from the skeletal system, the impact to the extracellular fluid is the same, a net increase in its concentration.

c) Countermeasure Studies

The final subtask to be performed in the calcium metabolic area was to supplement the analyses of the experimental bed-rest studies with an additional analysis of studies that investigated a select set of

countermeasures. The countermeasures selected for analysis were those that involve dietary manipulations of calcium and phosphorus during the bed-rest period.

Most of the experiments designed for investigating physiological changes during exposure to hypogravic environments involve small sample sizes. Resource and cost considerations limit the number of subjects available for experimental studies which, in turn, greatly limits the amount of data obtained and the statistical "power" of the results derived. Under these restrictions, careful analyses are essential in order to extract the maximum amount of information with acceptable accuracy. In an effort to improve the power of the statistical analyses and to consider the role of the experimental protocol in these analyses, a report concerning small sample statistics (36) was used to judge the applicability of certain statistical tests in the Bed-Rest Analysis Software System (BRASS). BRASS is the program used to analyze the bed-rest data.

Two of the USPHSF bed-rest studies investigated the dietary supplementation of phosphorus and three examined the impact of simultaneous dietary calcium and phosphorus supplementation during bed rest. None of the bed-rest studies investigated the effect of supplemental dietary calcium apart from dietary phosphorus. Consequently, the data analyses revolved around the influence of dietary phosphorus supplementation with the influence of dietary calcium supplementation assumed only if the experimental results deviated significantly from the phosphorus results.

The statistical sample sizes of these analyses are very small. A total of 11 subjects participated in the two studies containing supplemental dietary phosphorus protocols. Five of the subjects received a daily supplement of 83 percent of their baseline intake during specified times of the bed-rest period. Three received their supplement during the first twelve weeks of bed rest, while the other two received their supplement during the second twelve weeks. Of the remaining six subjects, two received a daily phosphorus supplement of 37 percent of their baseline intake while the two others received 5 and the last two received 0 percent increases. Consequently, most of the analyses are based upon the averaged results of two subjects. As a

point of reference, the experimental results derived from these analyses are compared to average bed-rest results established in a previous analysis of bed-rest only data (5).

The most notable results of the bed rest and supplemental phosphorus analyses are the effects of dietary phosphorus intake rates on the urine calcium excretion rates. In Figure 4-3, urine calcium excretion rates (in terms of the weekly deltas from the ambulatory average) are plotted as a function of time for five separate bed-rest studies. Three of the studies are illustrated in Panel A of Figure 4-3, where the subjects received 0, 5, and 37 percent higher rates of dietary phosphorus during bed rest than during the ambulatory, control period. Panel B of Figure 4-3 compares the results of these subjects receiving a 0 percent increase in dietary phosphorus with the average calcium excretion rate from the previous analyses of bed rest only data (5). The impact of the 83 percent phosphorus supplements during selected periods of the bed-rest phase are demonstrated in Panel C of Figure 4-3.

These results suggest that high and low doses of supplemental phosphorus appear to exert paradoxical effects on the urine calcium excretion rate. Low doses (less than 40 percent increase in dietary phosphorus) appear to enhance, while high doses (greater than 83 percent) appear to inhibit the already stimulated renal calcium excretion rates. The influence of the high dose on the renal excretion rate is very rapid since a noticeable inhibition is measurable within the first data collection period. In addition, the suppression of the urine calcium excretion rate is quite dramatic; the excretion rate decreases to a rate equivalent to or below the average rate recorded during the ambulatory, control period.

Despite the changes in the renal calcium excretion rates, some of the other elements in the calcium metabolic system appear to be unaffected. Significant changes in the plasma calcium concentrations were not recorded. Changes in the urine excretion rates of hydroxyproline, an indirect indicator of bone resorption rates, also remained unaffected by dietary phosphorus manipulations. In addition, most of the studies suggest that fecal calcium excretion rates are unaffected although high phosphorus doses administered

**URINE CALCIUM EXCRETION RATES (DELTA FROM AMBULATORY AVERAGE)
DURING BED REST AND SUPPLEMENTAL DIETARY PHOSPHORUS (+ DIET Pi).**

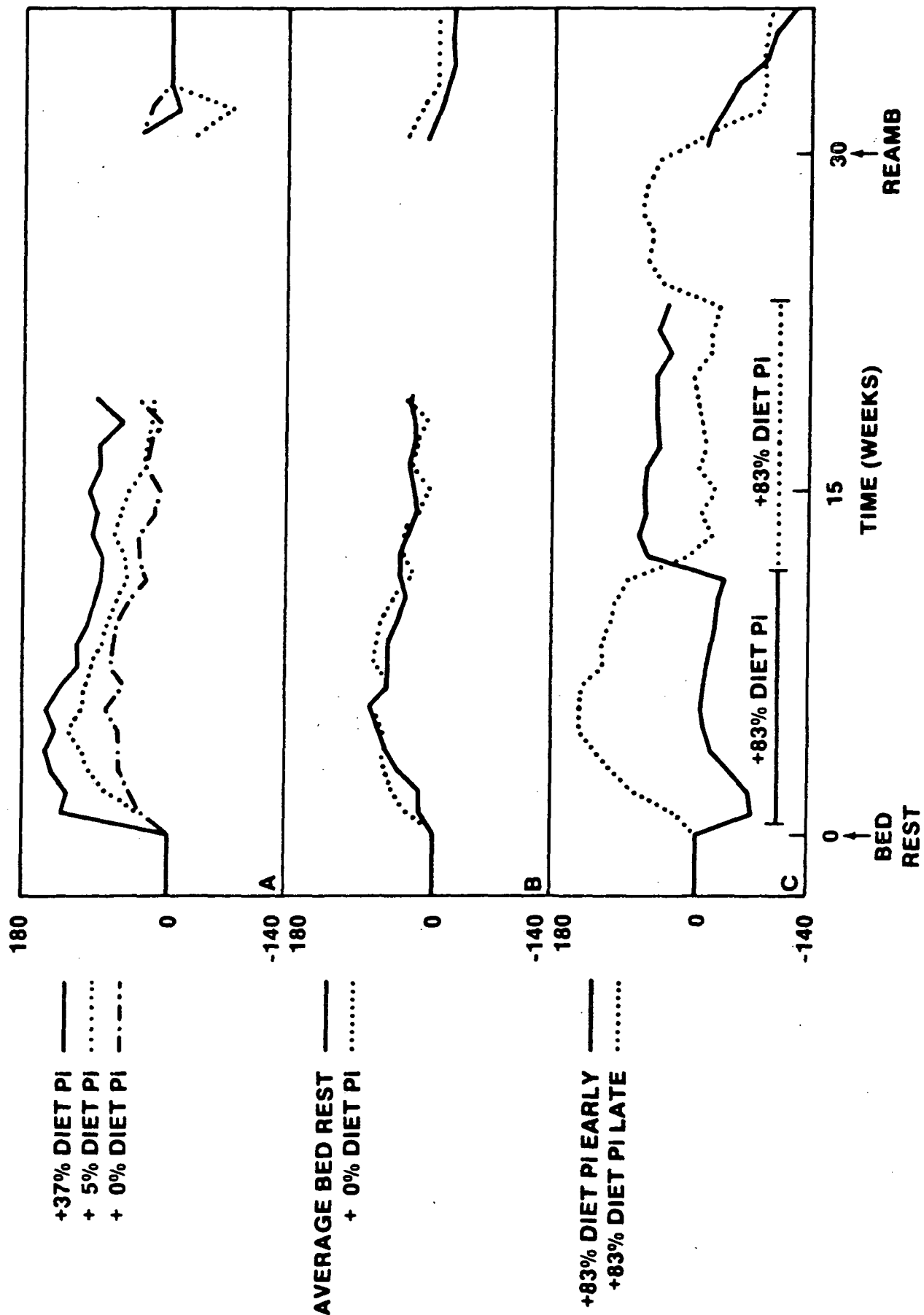


FIGURE 4-3

late in the bed-rest period may suppress average rates of fecal calcium loss. Measurements of hormonal changes, particularly the plasma concentrations of PTH and selected metabolites of Vitamin D were not collected.

As expected, urine and fecal phosphorus excretion rates increased as the supplemental dietary dose of phosphorus increased. The urine excretion rates rose by 2, 6, and 100 percent as the dietary loads increased by 5, 37, and 83 percent, respectively, above the ambulatory, control rates. Concurrently, the fecal excretion rates increased by 20, 50, and 70 percent above ambulatory values. The plasma phosphorus concentrations appeared to be unaffected by dietary loads. These data simply demonstrate that the dietary phosphorus supplements were in excess of physiological requirements and were excreted from the body.

The above data tend to suggest that high doses of supplemental phosphorus, in excess of 80 percent above daily baseline intake rates, may prevent the loss of total body calcium, evidenced by negative calcium balances, which have been recorded during exposure to hypogravic environments. Conversely, low doses of phosphorus may promote the negative calcium balances. Unfortunately, the mechanisms by which this suppression or enhancement may be occurring are unclear.

Of the parameters which determine the calcium balance (assuming changes in the sweat rates are negligible), only the urine excretion rate appears to be affected. This means that the calcium input rates are constant so changes in the renal excretion rates must be obtained from or stored into an internal calcium reservoir. The largest calcium pool in the body is the bone which contains about 98 percent of the total body calcium. If bone resorption increases during bed rest, as the urine hydroxyproline data suggests (5), then the rate of resorption is unaffected by dietary phosphorus manipulations. With high phosphorus doses, this hypothetically means that calcium is being removed from one part of the bone and, since it is not being excreted, probably is being stored in another part of the bone. Whether calcium is deposited into the bone as new hydroxyapatite material, or is simply stored as amorphous material is unclear. However, the rapidity with which the renal

calcium excretion rate responded to changes in the dietary phosphorus loads suggest that the calcium was stored in a readily available form and not deposited as hydroxyapatite material.

The relationship of the calcium and phosphorus metabolic systems are not fully understood. In an effort to theoretically clarify some of these relationships, a simulation of bed rest and a high phosphorus diet was executed on the model. During the simulation, the high phosphorus diet (+83 percent initialization) the phosphorus metabolic system resulted in rapidly increasing urine phosphorus excretion rates. The plasma phosphorus concentration rose slightly and inhibited the production rate of 1,25-(OH)₂D in the kidney. The reduction in the plasma concentration of this Vitamin D metabolite resulted in a long-term inhibition of the intestinal calcium absorption and thereby reduced the negative calcium balance late in the simulated bed-rest period. Of interest, however, is the fact that the model did not demonstrate a significant reduction in the rate of urine calcium excretion. This is contrary to the experimental results illustrated in Panel C of Figure 4-3 and demonstrates that the mathematical interrelationships between the calcium and phosphorus metabolic systems within the model are not complete.

4.4 CONCLUSIONS

The work accomplished in the calcium area during this contract period has been very exciting. The expanded version of the calcium model, with an improved bone system and a new phosphorus system, is fully operational. Several simulations, aimed at testing the model responses and comparing the variable output to actual experimental data, have been executed and have yielded excellent results. Although the original calcium model has been useful in testing and developing hypotheses of calcium metabolic changes during bed rest and space flight, this model provides the detail and specificity required to expand these analyses beyond the limits of the original model.

In the last two years a number of papers reporting the results of investigations concerning skeletal changes in animal species during simulated hypogravic conditions have been published. The expanded calcium model is an

analytical tool which can be used to examine hypothetical skeletal and metabolic implications inherent within the hypotheses. In addition, other hypotheses may be tested. Simulation analyses provide theoretical avenues for addressing questions involving highly interactive events within the system and for highlighting the next series of questions to be asked. Prophylactic and therapeutic countermeasure treatments may be proposed and assessed for feasibility with the model prior to expending vast resources for conducting the research. In addition, this type of simulation work can contribute to the development of ideas for experiment proposals and experiment designs. However, interspersed within the simulation analyses is a requirement for an interactive relationship with experimental research programs and data. The simulation data should be frequently tested with actual experimental data.

Other modeling techniques are available to examine the intricacies of the model itself such as sensitivity analyses. Sensitivity analyses define the quantitative relationships calculated within the system, as well as the magnitude and trend of model output generated by a change in critical parameters. This provides the ability to conduct a detailed analysis of model function. The model also may be modified to represent specific animal species and thereby test and compare differing metabolic responses to experimental stresses specific to human and other animal models. This is similar to the idea implemented by Nordheim (38) for the erythropoiesis model.

In summary, mathematical modeling is a useful tool for theoretically assessing and testing a wide variety of hypotheses specific to the system, intraspecies differentiations, and potential countermeasures. Two promising models have been developed and are ready for use by NASA.

5.0 POTENTIAL CONTRIBUTIONS OF PHYSIOLOGIC MATH MODELS TO FUTURE FLIGHT EXPERIMENTS

This section of the final report addresses Task 3 of the Statement of Work. Task 3 states that "the contractor shall conceive, design, and test key body fluid and blood volume regulation experiments by simulation." Since the statement of work was issued, several key fluid/electrolyte experiments have been conceived by NASA investigators in an effort to help design a Space Station Life Sciences Laboratory. These candidate experiments are contained in the NASA/JSC draft document "Human Research Facility Science Requirements for Space Station," dated January 1985. It seemed appropriate to utilize these as baseline experiments for this contractual task and to apply computer simulation to help design and test them.

Each of the experiments is presented below, first by stating its title and major hypothesis and then by a discussion of how previously developed mathematical models could enhance the experiments. In several instances, computer simulations were performed as examples of this application.

5.1 EXPERIMENT A: MEASUREMENT OF VENOUS PRESSURES AND PLASMA VOLUME Hypothesis

Venous pressure decreases within a day after weightlessness is achieved, and plasma volume decreases later. Each reaches a level at which it is maintained for the rest of the flight.

Current fluid/electrolyte physiologic models, of which the Guyton model is most prominent, are able to simulate changes in both central venous pressures (CVP) and plasma volume (PV) reasonably well. It is also capable of simulating both short and long-term events, as well as gravity-dependent stresses. This experiment is, therefore, an ideal subject for simulation using the Guyton model.

We simulated zero-gravity with the Guyton model by placing the "subject" in a head-down tilt of minus six degrees after seventy-two hours of rest. Figure 5-1 shows the simulated changes in upper body central venous pressure and plasma volume over a six month course of head-down tilt. Figure 5-2 is an expansion of hours 50-150 and shows in detail the acute changes that take place when the model is placed in head-down tilt at hour seventy-two.

SIMULATED CHANGE IN VENOUS PRESSURES AND PLASMA VOLUME DURING LONG DURATION
HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

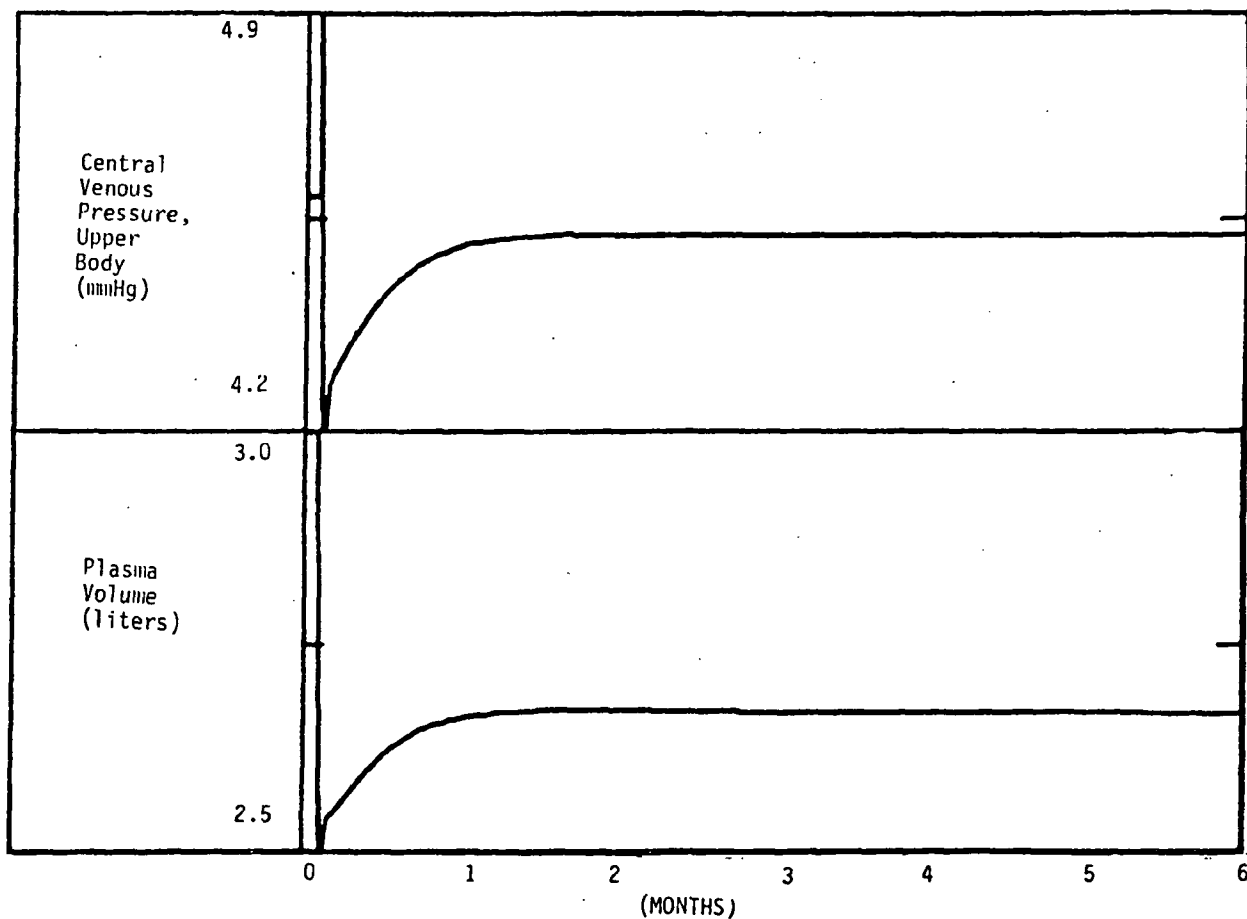


FIGURE 5-1

SIMULATED CHANGE IN VENOUS PRESSURES AND PLASMA VOLUME DURING LONG DURATION
HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

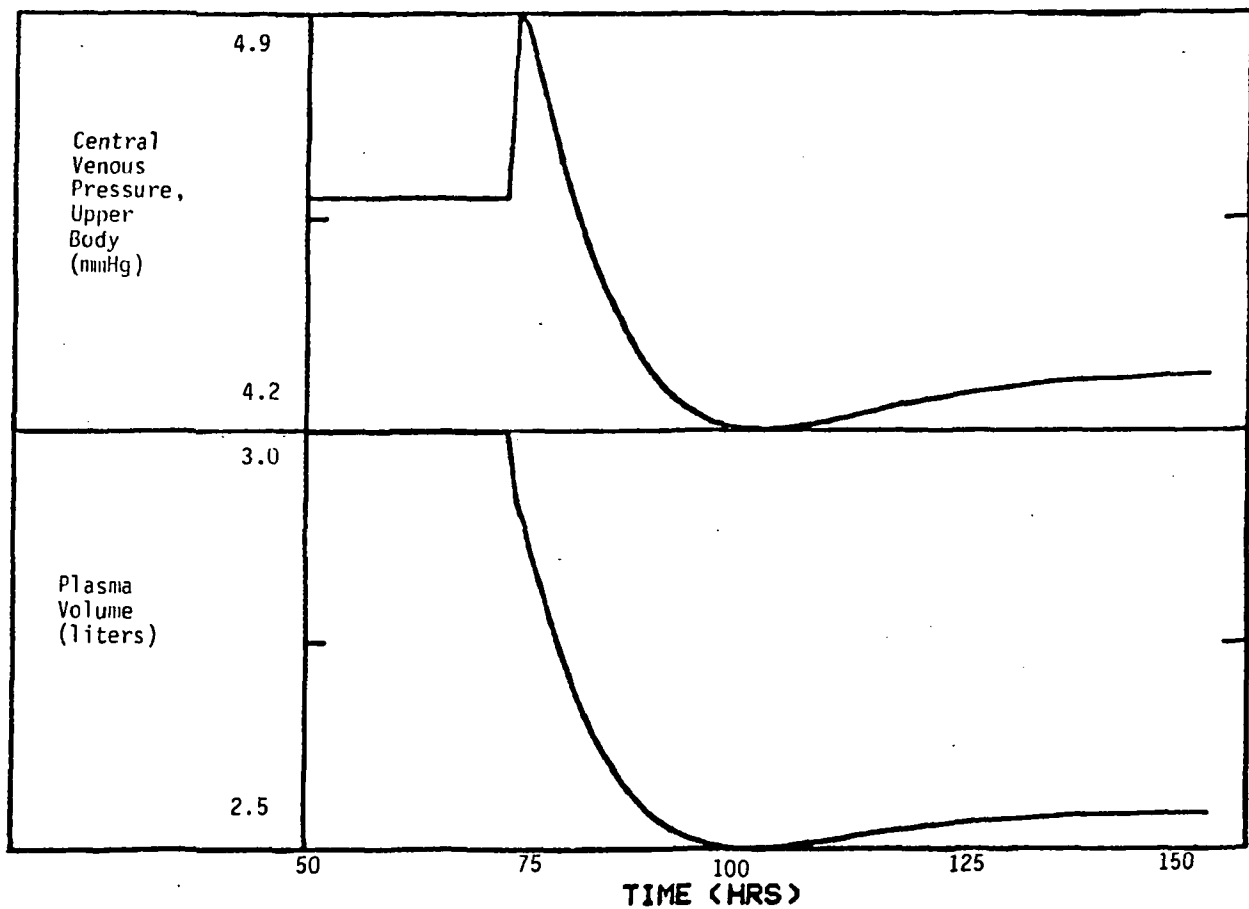


FIGURE 5-2

Placing the model in head-down tilt causes a rapid increase in central venous (right atrial) pressure which is followed by a gradual loss of plasma volume. The CVP then falls as plasma volume is lost and returns to baseline eight hours after being placed in head-down tilt. The CVP continues to fall for another twenty hours at which point both plasma volume and CVP begin to rise again. This gradual increase in CVP and plasma volume continues for about forty days until a new steady state is reached. Both parameters then remain stable for the remainder of the simulated six-month flight.

This simulation can help in the design of Experiment A by identifying key data points in the curves of the desired parameters. For instance, the model shows CVP's maximum value to be the first data point after head down tilt is initiated. This would imply that CVP reaches its maximum as soon as the subject enters a zero-g environment and suggests that CVP be measured as soon as possible after orbit is achieved. Additional graphs showing CVP as a function of plasma volume may also be plotted in an attempt to discern a cause-and-effect relationship.

Our simulation of Experiment A appears to give realistic data. If the actual experimental data does verify our simulation, then we could rely on our model to provide additional insight about parameters that were not measurable inflight. For instance, the Guyton model could provide data points for cardiac output and total body water and it would be possible to examine relationships between these parameters and the verified plasma volume and CVP parameters. Another use of the model would be to provide an extrapolation of the verified data curves. For instance, Experiment A calls for the CVP to be measured weekly for twelve weeks. As central venous catheter sites must be changed at least weekly, it seems unrealistic to schedule repeated central venous line placements on human subjects in space. The model, however, can extrapolate the verified one week curve to twelve weeks and beyond. One or two real data points might be collected during the twelve-week period in order to verify the simulated data. Thus, computer models are useful not only for providing insight into complex relationships between physiologic parameters, but also should give realistic extrapolation of previously verified data curves.

5.2 EXPERIMENT B: CIRCADIAN RHYTHM OF PLASMA HORMONES AND ELECTROLYTES DURING WEIGHTLESSNESS.

Hypothesis

Circadian rhythms change little in the space station environment, although there is a loss of amplitude of high and low measurements ("damping").

Although our current models do simulate ADH, angiotensin, aldosterone and the electrolytes mentioned in this experiment, they do not attempt to simulate circadian rhythms and thus would not be directly applicable for the purposes of this experiment. Computer models of circadian rhythms do exist, but any effort undertaken to incorporate a circadian system into such complex physiologic models as Guyton's must be viewed as a major project. The problem of simulating the light/dark and work/rest cycles aboard space station would only complicate the matter. Nevertheless, data from inflight circadian rhythm experiments such as the one scheduled to fly aboard Spacelab-4 may be of significant help in designing a circadian model. There is no doubt that a better understanding of circadian rhythms would be of great help to NASA in scheduling crew duty cycles for long-duration missions. Physiologic modeling can provide the necessary framework to perform a systematic analysis of the problem in order to gain that better understanding.

5.3 EXPERIMENT C: EARLY AND LONG DURATION EFFECTS OF WEIGHTLESSNESS ON SELECTED ENDOCRINE PARAMETERS IN PLASMA AND URINE: ANTIDIURETIC HORMONE, HUMORAL NATRIURETIC SUBSTANCES, CORTISOL

Hypothesis

Plasma and urinary antidiuretic hormone (ADH) and cortisol increase on the first day of weightlessness and then return to normal or decrease. Plasma and urinary natriuretic hormone increase later than ADH does and remain increased during weightlessness. Rate of excretion of sodium, potassium, chloride, calcium and phosphate vary with the time of day, but are generally increased over preflight levels. Rate of excretion of fluid is increased during most of the flight.

The essential design of this experiment is the measurement of several key hormones and electrolytes every four hours during the first week in space. The model can simulate several of these parameters. Figure 5-1 shows our model's estimate of plasma volume over a six-month course of head-down tilt (see Figure 5-2 for details of acute changes). Comparing these graphs with

Figure 5-3 (change in total body water during six months of head-down tilt) and Figure 5-4 (change in total body water during the first three days of head-down tilt), it appears that about 40-50 percent of the loss in total body water is due to the decrease in plasma volume. Figures 5-5 and 5-6 show the responses for serum sodium concentration and the rate of renal sodium excretion. The simulation predicts that sodium excretion rises to ten times the baseline rate immediately after initiation of head-down tilt and remains elevated for approximately fifteen hours. This is undoubtedly related to the increased central venous pressure resulting from the cephalad fluid shift which the body interprets as fluid overload. The serum sodium concentration, however, never differs by more than 0.8 mEq/l from its preflight (pre-tilt) baseline. Although this may indeed be realistic, it may also represent an excessively tight control over serum sodium concentration regulation at the expense of urine sodium concentration and aldosterone/ADH regulation.

Other parameters shown for Experiment C include serum potassium concentration, total extracellular potassium, and renal potassium excretion (Figure 5-7, details of acute changes on Figure 5-8). Serum potassium concentration initially rises, as does serum sodium concentration, probably as a result of the decreased ADH. The low ADH level contributes to a high excretion of free water which results in an initial elevation of all serum electrolyte concentrations. The hyperkalemia lasts much longer than the hypernatremia, something one would expect in an environment sensing fluid overload. Nevertheless, the model keeps the serum potassium concentration within physiologic limits. Total extracellular sodium, 75.2 mEq pre-tilt, finally reaches a new steady-state of 72.2 mEq after fifty days of head-down tilt. Six-month curves for ADH concentration and aldosterone concentration are shown in Figures 5-9 and 5-10. Although these values have yet to be verified by actual head-down tilt, the use of the model as a template for experimental design is readily apparent.

While these simulations and the relationships between these variables are basically correct, they do not all support the hypothesis given earlier for Experiment C. For example, renal excretion of fluid and electrolytes all return to normal in contrast to the hypothesis (and the Skylab data) which demonstrates an increase in these factors. In contrast, a previous simulation

SIMULATED CHANGES IN TOTAL BODY WATER, GFR, AND RENAL BLOOD FLOW DURING LONG-DURATION HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

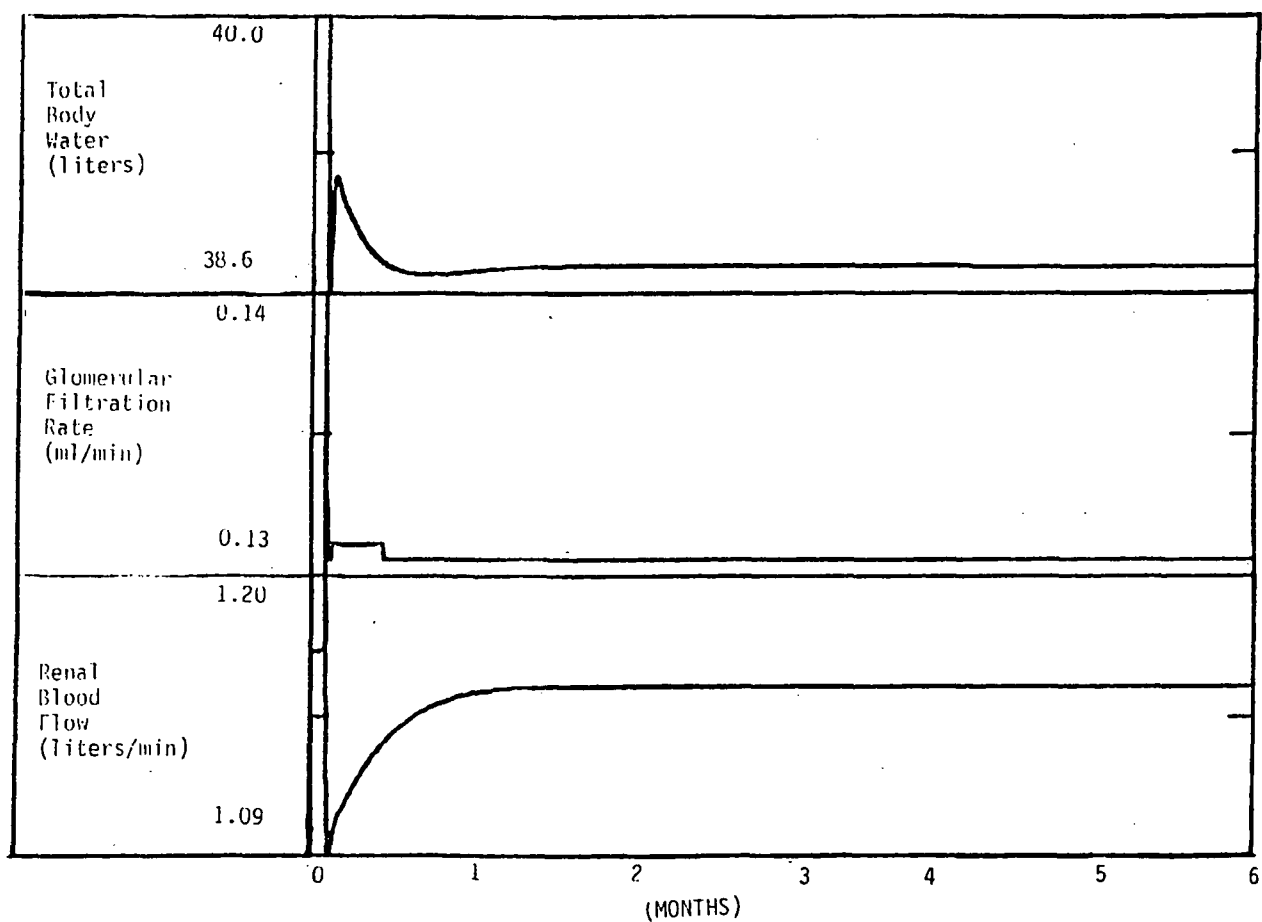


FIGURE 5-3

SIMULATED CHANGES IN TOTAL BODY WATER, GFR, AND RENAL BLOOD FLOW DURING LONG DURATION HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

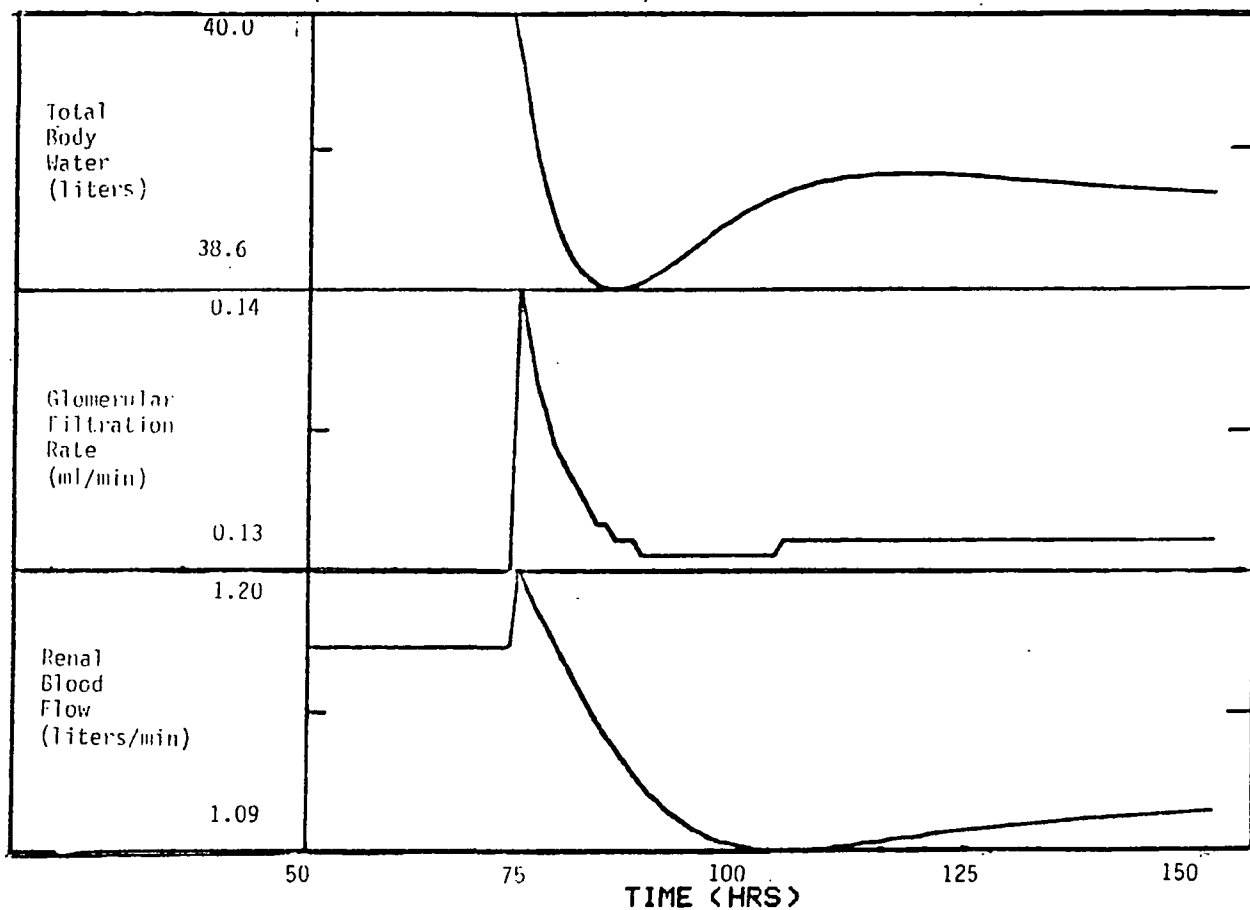


FIGURE 5-4

SIMULATED CHANGE IN SERUM SODIUM CONCENTRATION AND RENAL SODIUM EXCRETION
DURING LONG DURATION HEAD DOWN TILT (INITIATED AT HOUR 72)

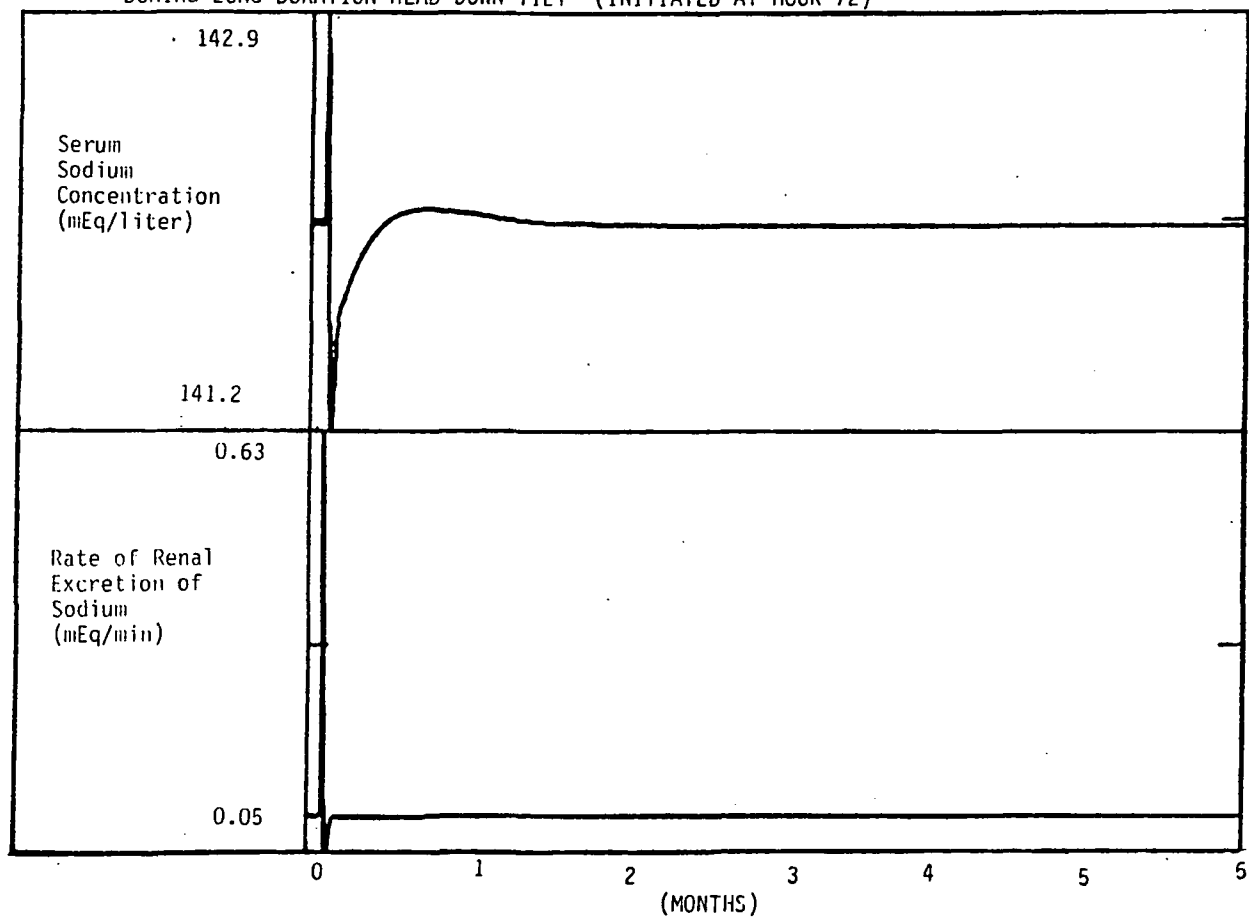


FIGURE 5-5

SIMULATED CHANGE IN SERUM SODIUM CONCENTRATION AND RENAL SODIUM EXCRETION
DURING LONG DURATION HEAD DOWN TILT (INITIATED AT HOUR 72)

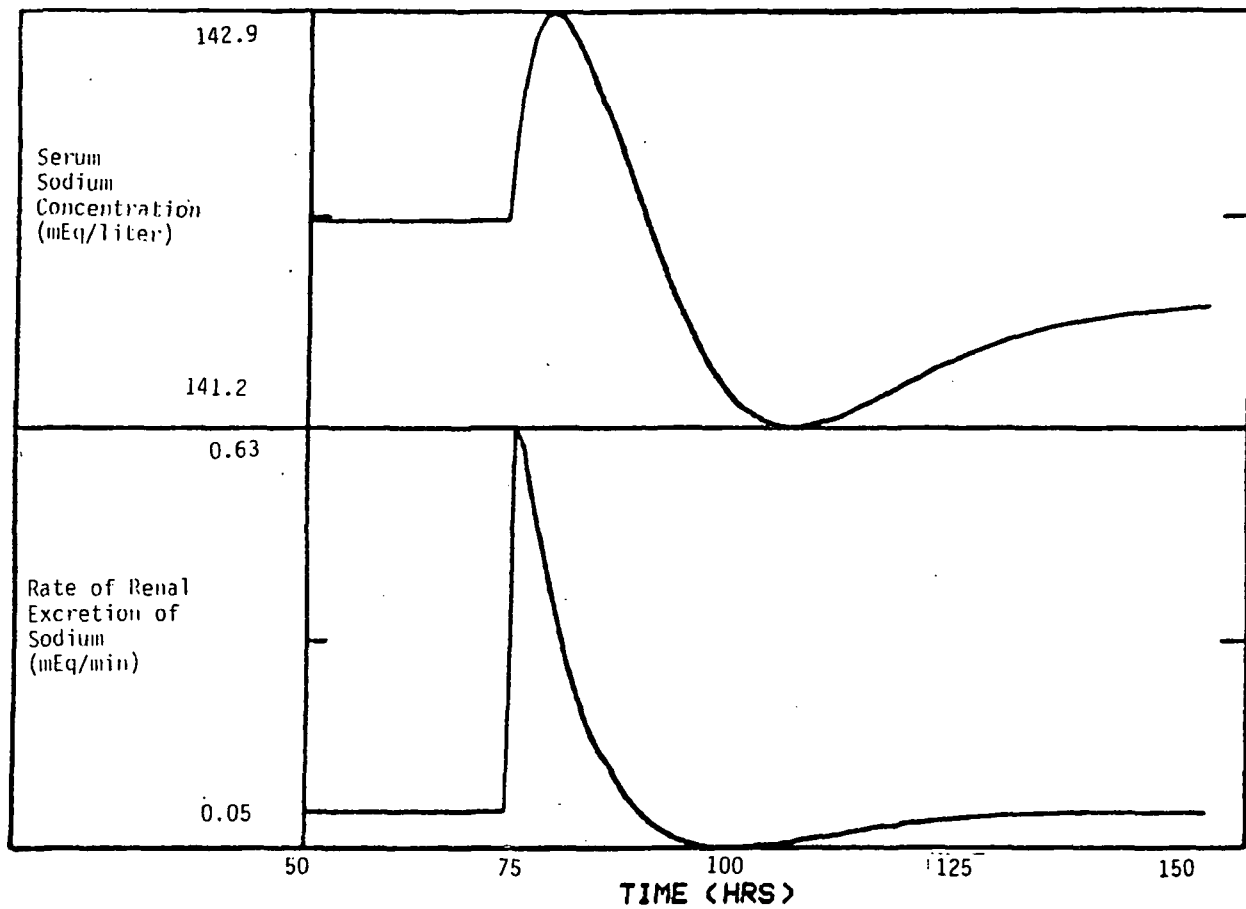


FIGURE 5-6

SIMULATED CHANGE IN EXTRACELLULAR POTASSIUM LEVELS AND RENAL POTASSIUM EXCRETION
DURING LONG DURATION HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

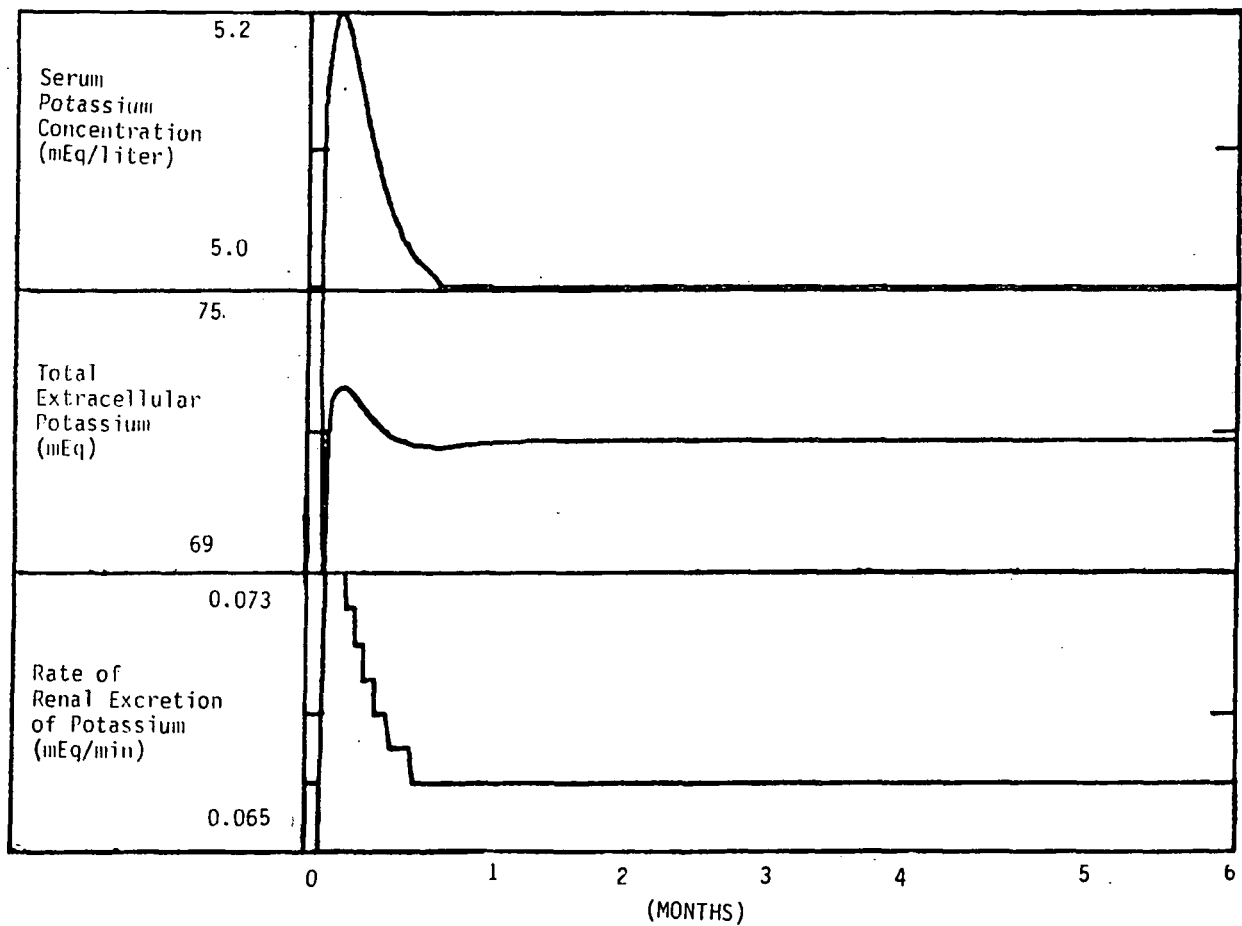


FIGURE 5-7

SIMULATED CHANGE IN EXTRACELLULAR POTASSIUM LEVELS AND RENAL POTASSIUM EXCRETION
DURING LONG DURATION HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

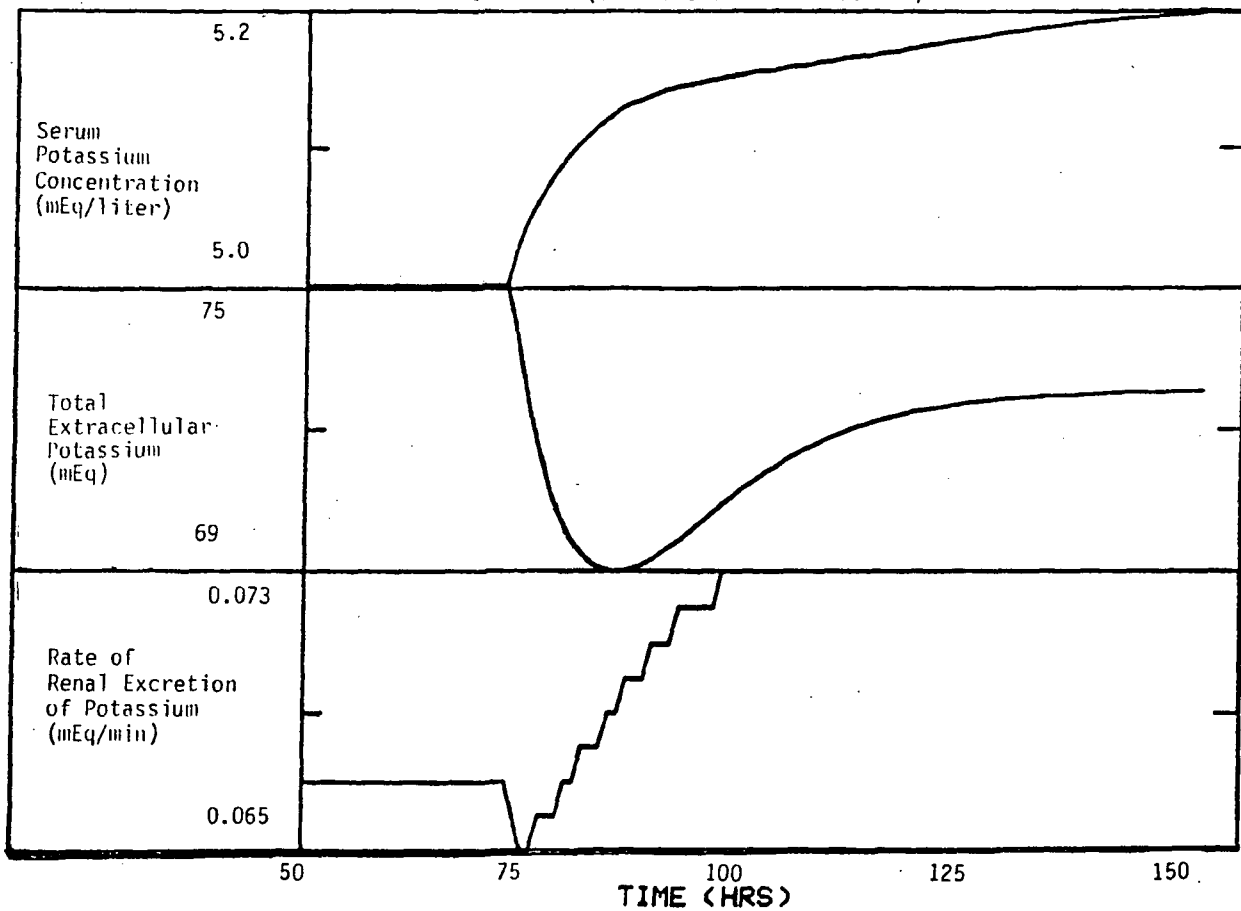


FIGURE 5-8

SIMULATED CHANGE FOR ANTIDIURETIC HORMONE (ADH) AND ALDOSTERONE DURING LONG TERM HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

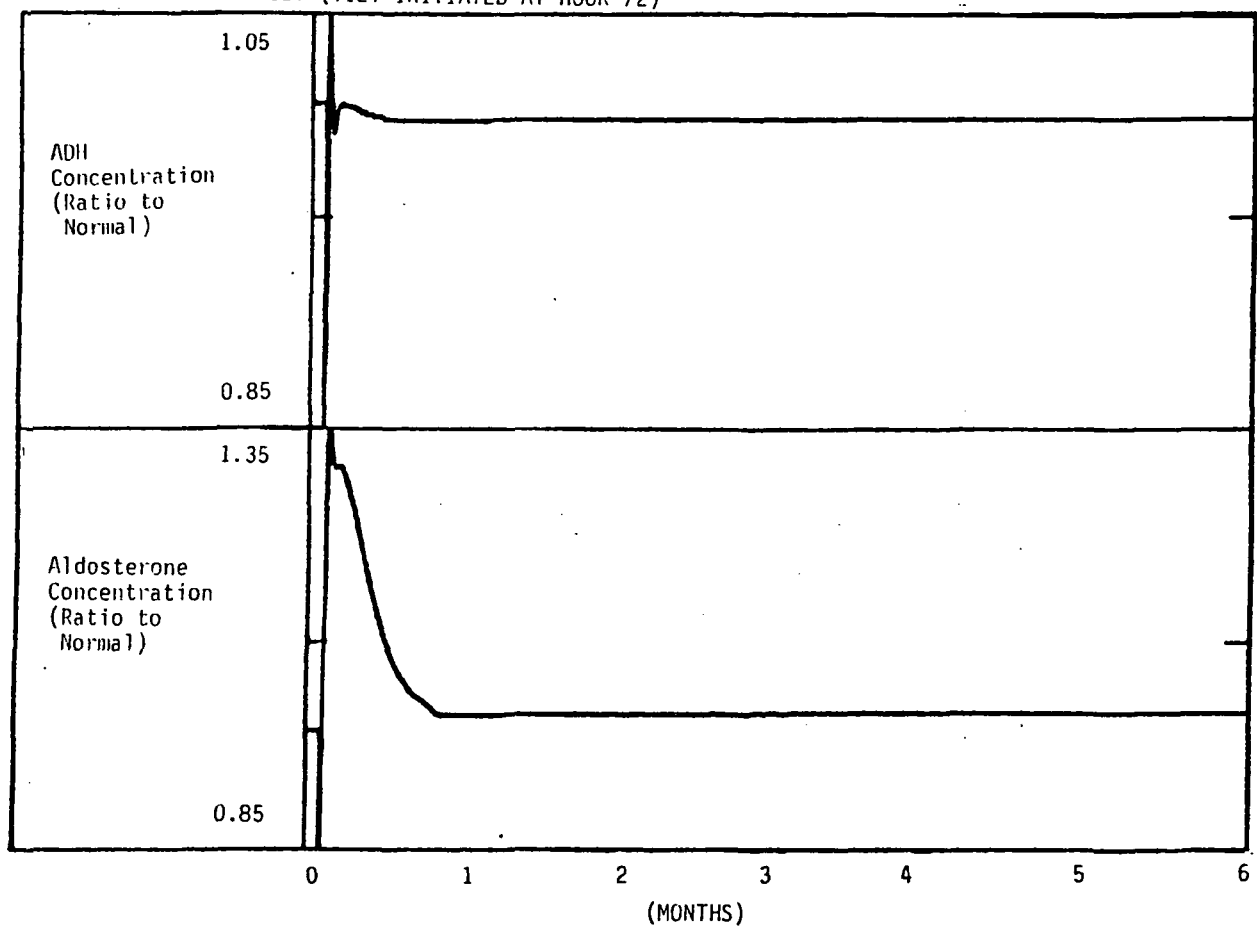


FIGURE 5-9

SIMULATED CHANGE FOR ANTIDIURETIC HORMONE (ADH) AND ALDOSTERONE DURING LONG TERM HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

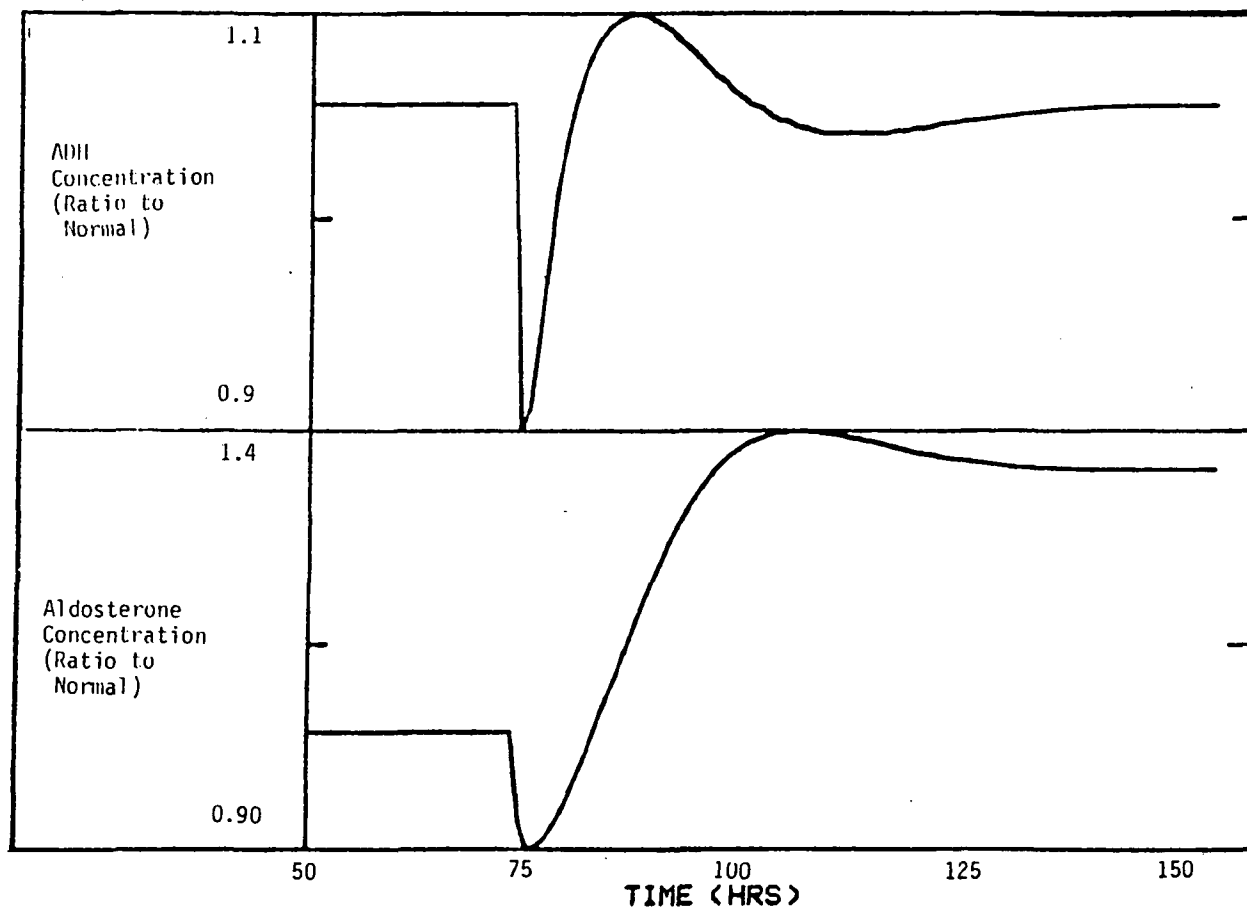


FIGURE 5-10

study (9) demonstrated a much closer agreement with the Skylab data for renal and endocrine measurements than was shown above. A portion of the results from the 1977 study are shown in Figure 5-11. These results indicate increases in fluid, sodium and potassium excretion, decreases in ADH and increases in aldosterone and angiotensin, as predicted by the hypothesis of Experiment C. The primary reason for this degree of accuracy was in the assumption that total skin losses (sweat + insensible losses) were lower than preflight. A secondary factor was the assumption of a natriuretic agent. Both of these hypotheses were incorporated into the model prior to simulation.

5.4 EXPERIMENT D: EFFECTS OF WEIGHTLESSNESS ON ADRENAL AND KIDNEY INTERACTION

Hypothesis

The effects of weightlessness on renal function precede its effects on the renin-angiotensin-aldosterone system.
Norepinephrine and prostaglandin mediate some of the effects.

Major adrenal-kidney interactions include induced renin release induced by norepinephrine (secreted by the adrenals), as well as the direct renal effects of corticosteroids. As the Guyton model does not simulate cortisol or norepinephrine it would not be useful for determining most adrenal-kidney interactions without some modifications. However, it does simulate a variety of renal parameters. Many of the desired parameters have been discussed in the previous experiments. The two major renal parameters simulated in this experiment are Renal Blood Flow (RBF) and Glomerular Filtration Rate (GFR). The simulated curves for the changes in RBF and GFR during prolonged head-down tilt are interesting (Figures 5-9 and 5-10). The RBF curve looks quite believable, as the initial increase due to the body's central hypervolemia gives way to sub-baseline values which are probably secondary to the combination of a contracted intravascular volume and the direct hydrostatic effects of a minus six degree position. The GFR curve is harder to explain and one would have to carefully analyze the inner workings of the model to ascertain why the GFR remains above the pre-tilt baseline despite the volume depletion and head-down tilt. Curves for renin and angiotensin II (Figures 5-12 and 5-13) appear to respond fairly well to the various states of hydration, although it is not clear why renin concentration achieves a

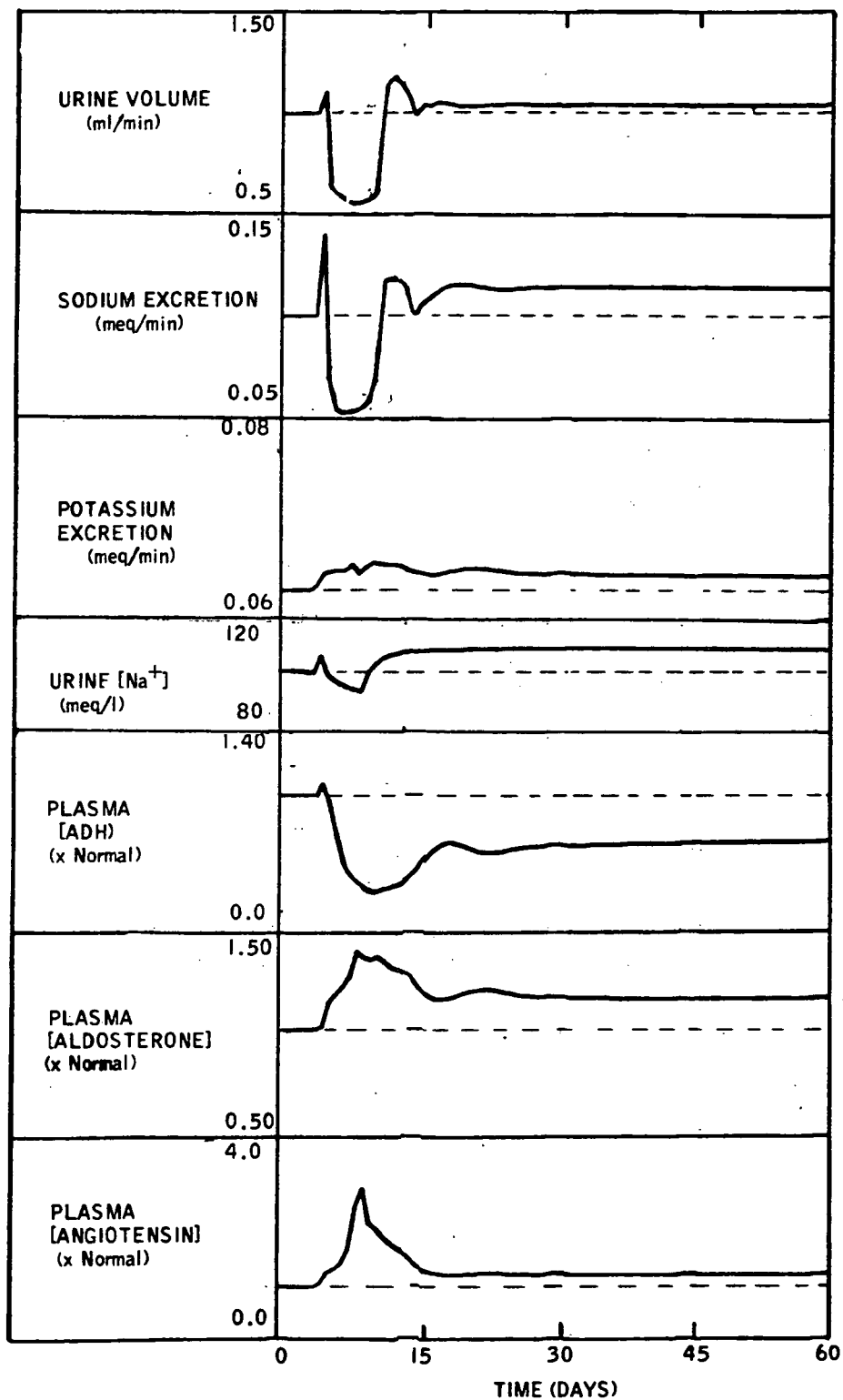


FIGURE 5-11

INTEGRATED HYPOTHESES SIMULATION OF COMPOSITE SKYLAB MISSION

SIMULATED CHANGE IN RENIN AND ANGIOTENSIN II DURING LONG TERM
HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

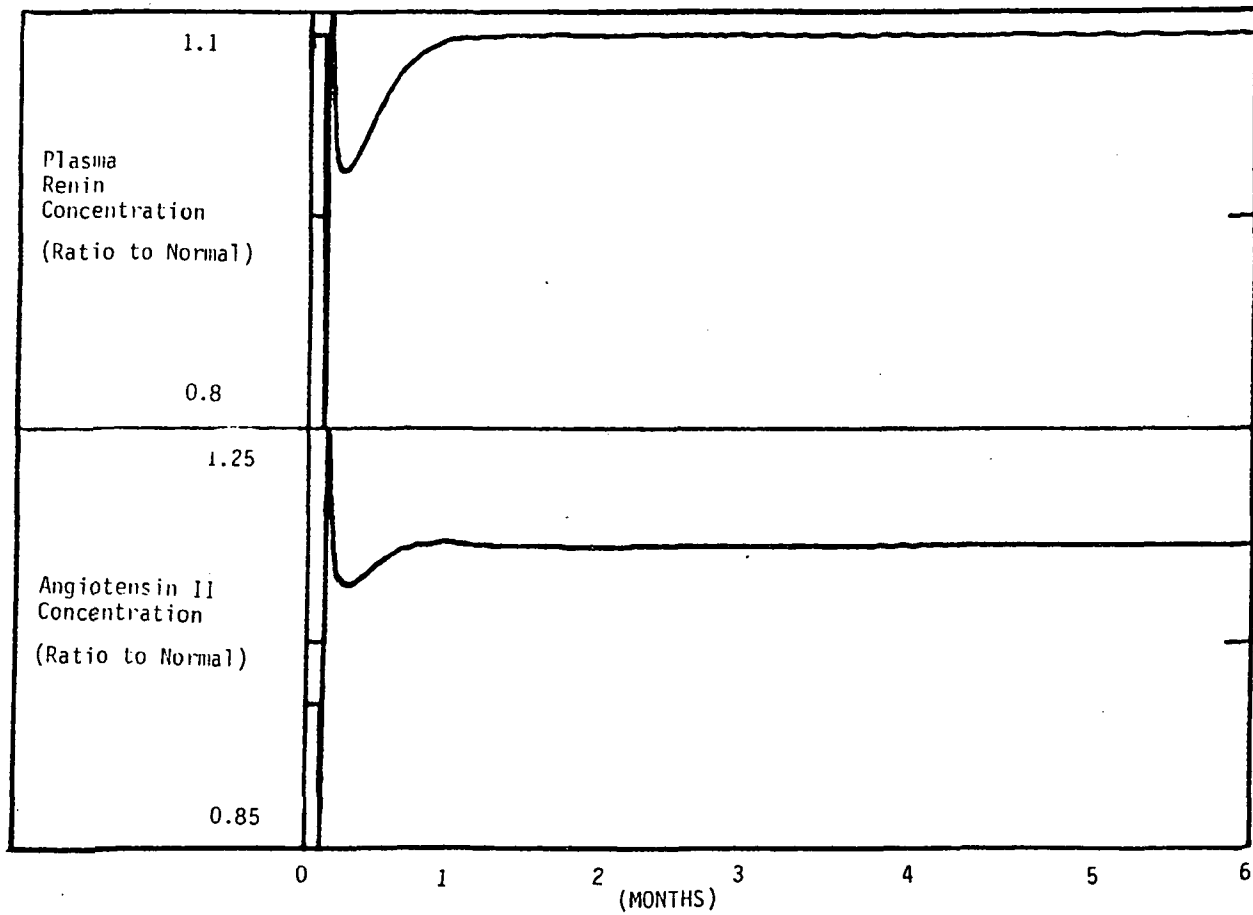


FIGURE 5-12

SIMULATED CHANGE IN RENIN AND ANGIOTENSIN II DURING LONG TERM
HEAD DOWN TILT (TILT INITIATED AT HOUR 72)

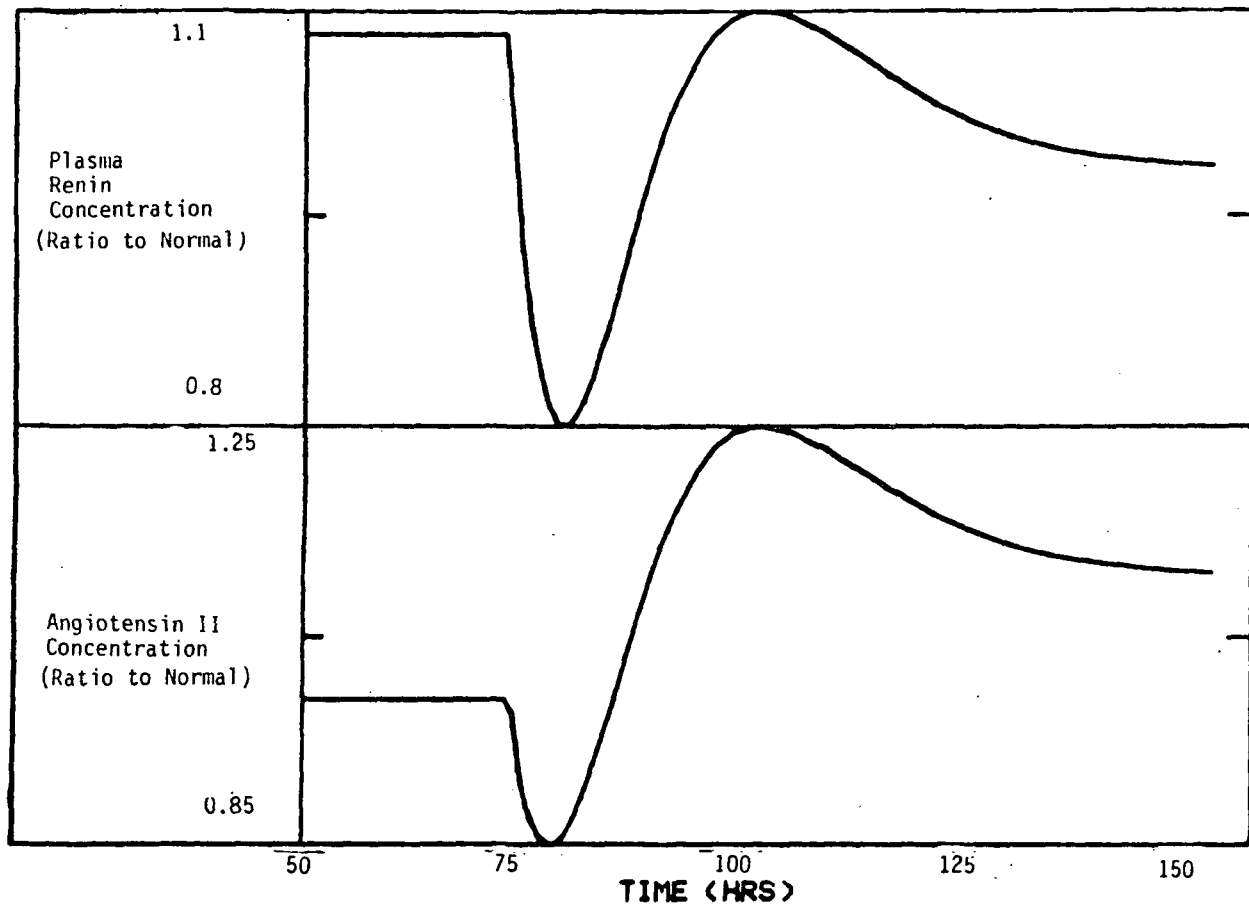


FIGURE 5-13

steady-state level lower than the pre-tilt baseline while the new steady-state level for angiotensin II is above the preflight baseline.

Although this demonstrates some of the limitations of the model as it currently exists, it provides us an opportunity to test our current physiologic theories about adrenal-renal interactions, the renin-angiotensin-aldosterone axis, and factors affecting GFR and RBF by incorporating them into the model. The task of updating and verifying mathematical models of physiologic systems would be simplified by using such state-of-the-art tools as rule-based languages or symbolic programming. In addition to updating the models to test current physiologic theories, we should also try to get the models to simulate zero-g as accurately as possible. The models currently attempt to simulate zero-g by simulating supine bed rest, head-down tilt or lower body positive pressure. For instance, supine bed rest might be currently simulated by raising mean capillary filling pressure (MCFP), which, in turn, initiates a series of further events. A more accurate simulation of zero-g may be accomplished by not only resetting MCFP but adjusting venous compliance and pulmonary ventilation-perfusion mismatch as well. A new model specifically designed for direct zero-g simulation, as well as a detailed adrenal subroutine, may need to be developed before mathematical modeling analysis contributes significantly to complex areas like adrenal-kidney interactions.

5.5 EXPERIMENT E: LONG-TERM EFFECTS OF INCREASED ELECTROLYTE AND MUSCLE LOSS ON RENAL FUNCTION

Hypothesis

Stone-forming potential of crewmembers' urine will increase with time spent in space.

Experiment E again points out the difficulties of simulating zero-g situations with physiologic models as they are currently configured. The important problem of simulating the factors that may contribute to an increased risk of kidney stone formation during space flight requires a model with strong calcium-renal-fluid regulation interactions. At present, no model exists that can accurately estimate the risk of renal calculi formation. Such a model would have to accurately generate zero-g values for serum and urine calcium, phosphate, oxalate, uric acid, pH, etc. and then be able to integrate these factors to determine the risk of stone formation.

5.6 EXPERIMENT F: STUDY OF CORTICOSTEROID HORMONE METABOLISM IN WEIGHTLESSNESS BY USE OF PHARMACOLOGIC INTERVENTION

Hypothesis

Weightless subjects will respond in a normal manner (increase in production of 17-hydroxycorticosteroids) to drugs that decrease production of aldosterone and cortisol.

Experiment F is another example of an area of physiology not currently available for computer simulation. A mathematical representation of the hypothalamic-pituitary-adrenocortical axis could be developed, and the effects of drugs such as metyrapone could be simulated as well. But it needs to be emphasized that mathematical models cannot determine a priori whether or not suppression of the hypothalamic-pituitary-adrenocortical axis occurs in space. A certain amount of experimental data must first be gathered so that a model may be built upon it. Only after these data have been gathered and the model has been verified for that data can the model help investigators in determining hidden cause and effect relationships and predicting different outcomes under different circumstances. For instance, if a model is developed and verified to simulate neurohypophyseal-adreno-cortical interactions on the basis of data collected on flight days 0, 14, and 28, it will probably be useful in predicting values for flight days 35 and 42. The responses of the validated computer models may also provide new insights into the complex relationships between multiple physiologic parameters. Furthermore, a model would act as a repository for all of the facts, hypotheses, and inter-relationships of these complex biological systems.

5.7 EXPERIMENT G: EFFECT OF LOWER BODY NEGATIVE PRESSURE, WATER-SALT SUPPLEMENTS AND EXERCISE ON WEIGHTLESSNESS-INDUCED CHANGES IN ENDOCRINE AND ELECTROLYTE PARAMETERS

Hypothesis

Exposure of subjects to lower-body negative pressure (LBNP) prevents at least part of the increase in excretion of water and electrolytes that usually occurs during weightlessness.

Experiment G is an ideal application for modeling. The Guyton model has been modified by this contractor so that it can simulate LBNP and fluid loading. The connections that exist in the Whole-Body Algorithm between the Guyton model and the pulsatile cardiovascular model allow the user to look at both

long-term deconditioning as well as short-term beat-to-beat responses for a variety of LBNP/fluid load combinations. Various degrees of exercise may also be added to the protocol. The fidelity with which MATSCO's Whole-Body Algorithm simulates the cardiovascular system has been illustrated (25) by a study in which heart rate and blood pressure of the crew of STS-1 during reentry was simulated.

Experiment G is particularly illustrative because it can be shown that modeling is useful in designing operational countermeasure protocols in addition to helping design experimental protocols. For instance, because the models have been fairly well validated for reentry simulations, they would be able to assist with the design of a fluid load/g-suit protocol to counteract orthostatic intolerance during reentry (see Section 3.0). Rather than relying on anecdotal data, NASA could conduct an extensive analysis by means of simulation in order to determine the best protocol. Similarly, several combinations of LBNP/exercise/fluid load protocols may be simulated in order to identify those most promising for actual inflight experimentation. The effect of these protocols on vital parameters like heart rate, blood pressure and cardiac output could be readily obtained inflight. Model-generated parameters could then be validated once a suitable protocol has been chosen. Once these parameters have been validated, the model may be used to determine which of the parameters yet to be measured inflight appear most interesting, thus helping to design follow-up protocols. One can readily see how computer models can be used to develop a logical series of inflight experimental protocols, with each protocol being used to validate the model further. The model would help identify those parameters most likely to yield valuable new insights along each step of the way.

It is hoped that the above discussion of the seven Fluid and Electrolyte experiments mentioned in the January 1985 draft "Human Research Facility for Space Station IOC Science Requirements" has presented a balanced view of physiologic models and their potential contribution to the future of NASA's Life Science Program. We have attempted to show that models may be used to fill in the gaps of current knowledge by simulating those parameters not amenable to measurement inflight; that they are useful in extrapolating long-term data from short-term experiments; that they can aid in the design of

both one-time and sequential experimental protocols; that they can provide valuable insights into the complex relationships between multiple physiologic parameters; that they can systematically analyze a multitude of operational protocols in order to determine which ones are most likely to succeed; and finally, that they may be used as a sounding board with which investigators may test the latest physiologic theories, especially as they relate to space flight and the environment of zero-g.

6.0 REFERENCES

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APPENDIX B

Complete List of Technical Reports Associated With This Contract

<u>TIR No.</u>	<u>Date</u>	<u>Title and Author</u>
2114-MED-4001	7/84	Mathematical Modeling of Fluid-Electrolyte Alterations During Weightlessness - J. Leonard
2114-MED-4002	9/84	Predictions of Cardiovascular Responses During STS Reentry Using Mathematical Models - J. Leonard and R. Srinivasan
2114-MED-4003	9/84	Analysis of Head-Down Tilt as an Analog of Weightlessness Using a Mathematical Simulation Model - J. Leonard
2114-MED-4004	8/84	Quarterly Progress Report for Computer Simulation Studies in Fluid & Calcium Regulation and Orthostatic Intolerance - J. Leonard
2114-MED-4005	9/84	Statistical Analysis Techniques for Small Sample Sizes - S. Navard
2114-MED-4006	12/84	Quarterly Progress Report for Computer Simulation Studies in Fluid & Calcium Regulation and Orthostatic Intolerance - J. Leonard
2114-MED-4007	1/85	Simulation of G-Tolerance Curve Using the Pulsatile Cardiovascular Model - M. Solomon and R. Srinivasan
2114-MED-5001	3/85	Quarterly Progress Report for Computer Simulation Studies in Fluid & Calcium Regulation and Orthostatic Intolerance - R. Srinivasan
2114-MED-5002	5/85	The Behavior of Renal-Regulation Hormones During Hypogravic Stress - J. Leonard
2114-MED-5003	4/85	A Systems Analysis of the Erythropoietic Response to Weightlessness - Vol. I - Math Model Simulations ... - J. Leonard
2114-MED-5004	4/85	A Systems Analysis of the Erythropoietic Responses to Weightlessness Vol. II. Description of the Model of Erythropoiesis Regulation - J. Leonard

APPENDIX B (cont'd)

Complete List of Technical Reports Associated With This Contract

<u>TIR No.</u>	<u>Date</u>	<u>Title and Author</u>
2114-MED-5005	4/85	The Modeling and Simulation of Feedback Control Systems - J. Leonard
2114-MED-5006	4/85	Description, Validation, and Modification of the Guyton Model for Space-Flight Application - J. Leonard
2114-MED-5007	4/85	Alteration/Corrections to the BRASS Program - S. Brand
2114-MED-5008	5/85	Fluid-Electrolyte Responses During Prolonged Space Flight: A Review and Interpretation of Significant Findings - J. Leonard
2114-MED-5009	4/85	An Integrated Analysis of the Physiological Effects of Space Flight: Executive Summary - J. Leonard
2114-MED-5010	5/85	A Detailed Analysis of the Erythropoietic Control Systems Using a Species-Independent Model of Erythropoiesis - A. Nordheim
2114-MED-5011	5/85	Addendum to the STCAL and LTCAL User's Guide - S. Brand
2114-MED-5012	5/85	Analysis of the Effects of Countermeasures for Orthostatic Intolerance Using Computer Simulation - R. Srinivasan
2114-MED-5013	5/85	Effects of Weightlessness on the Cardiovascular System: A Review of Significant Findings from the Skylab Missions - R. Srinivasan
2114-MED-5014	5/85	Circulatory Changes in Bed Rest, Head-Down Tilt, and Space Flight: A Comparison - R. Srinivasan
2114-MED-5015	5/85	Final Report for Computer Simulation Studies in Fluid and Calcium Regulation and Orthostatic Intolerance - J. Leonard
2114-MED-5016	5/85	Space Flight Simulations of Calcium Metabolism Using Mathematical Models of Calcium Regulation - S. Brand

APPENDIX C

BIOMEDICAL PROBLEMS

GENERAL ISSUES

ADAPTATION TO ZERO-G

Assess the mechanisms involved during adaptation to weightlessness in the different physiological systems of the body.

PHYSIOLOGICAL LIMITS

Determine the limits of stay in space by assessing the time course and end points of processes involved in identified biomedical symptoms.

MULTIPLE EXPOSURES

Study the effects of repeated short-term exposures to space flight on specific physiological systems or psychological behavior with regard to measuring the relaxation time of these effects following flight, determining if the effects are cumulative, and assessing the optimal periods between flight exposures.

COUNTERMEASURES

Determine the countermeasures to biomedical problem areas that limit man's productivity and safety.

READAPTATION

Determine the processes of readaptation to Earth's gravity and discover methods to minimize adverse aspects of this condition.

CREW HEALTH

Determine the optimal training and physiological conditioning regimes that would maintain crew health during inflight exposure to zero-g and readaptation to one-g. These include considerations of exercise, diet, drug administration, biofeedback, or other mental exercise.

INDIVIDUAL VARIABILITY

Determine how weightlessness affects various types of individuals with special consideration given to factors such as age, gender, and physical condition.

ANIMAL MODELS

Develop appropriate animal models for conducting studies related to biomedical problems.

GROUND-BASED ANALOGS

Utilize space- flight experiments to verify hypothesis developed through ground-based analogs.

EQUIPMENT AND METHODS

Utilize state-of-the-art equipment and techniques to reliably perform critical measurements (primarily non-invasive) reflecting the adaptation processes in the context of testing and verifying a scientifically sound hypothesis.

HUMAN SUPPORT
MEDICAL SUPPORT AREA

Monitoring Diagnosis and Treatment

- o Develop and evaluate biomedical monitoring and testing procedures for space flight application which would provide significant information regarding the flight crew's medical status.
- o Develop clinical laboratory procedures, including analyses of biological fluids (blood/urine), which could be used under weightless conditions for routine biomedical evaluation and testing.
- o Develop diagnostic imaging equipment that operates in a gravity-free environment and which addresses a known biomedical problem developing from the adaptation process or some trauma/illness situation.
- o Determine if the incidence, treatment, and healing of trauma in weightlessness is identical to that in one-g.
- o Study the underlying basis of various medical treatments that have unique problems associated with them due to the weightless environment. Examples of such procedures include pharmacokinetic studies, wound, burn and fracture healing, fluid therapies, and responses to bleeding and clotting.
- o Determine if the pharmacokinetic processes (drug absorption, transport, metabolism, efficacy, excretion) of drugs administered in space are the same as those administered in one-g.
- o Study the effect of exercise on crew performance.
- o Study the effect of altered sleep/work cycles on crew performance.
- o Develop standards of normal crew health for the weightlessness environment.

BIOMEDICAL PROBLEMS

HUMAN FACTORS

CRITICAL ISSUES

- o Continued development of self-regulatory, health maintenance procedures, such as self monitoring of physiological health indicators, prescribed drug and exercise treatments, and biofeedback techniques, to contribute to the individual's physical and psychological adaptation to the space environment (for example, using biofeedback techniques to reduce or prevent symptoms of space motion sickness).
- o Determination of the relationship of tasks performed on Earth and those performed in space, in terms of time, energy, manpower, etc., to define optimal workloads and work schedules in the space environment.
- o Further development of procedures and techniques to predict and select individuals most adaptable to the zero-gravity environment, to the social and physical confinement and isolation of habitability in space, and to the work to be performed both as an individual and as a group member under space-flight conditions for extended durations.
- o Further development of procedures and techniques to optimally train, on Earth, individuals and groups to perform tasks proficiently and efficiently in the zero-gravity environment. This includes training manual dexterity, physical coordination, and muscular strength to each individual and physical orientation and coordination between two or more individuals to perform tasks that demand specific, acquired, zero-gravity skills.
- o Investigation of optimal spacecraft design to help individuals to adapt to the confined, isolated, and weightless environment of space flight and to provide leisure facilities for both recreation and privacy.
- o Investigation of spacecraft design as a tool to amend, or improve, task performances that are impacted by losses of sensory and perceptual discrimination in the space environment (such as depth perception in the presence of a black background, applying leverage in the absence of gravitational forces, and estimating the amount of force necessary to move an object from one location to another).
- o Development of a social and governmental structure to provide organizational and regulatory support to a group of individuals living in the confined and isolated environment of space for extended periods of time.

GENERAL PHYSIOLOGICAL AND BEHAVIORAL ISSUES

- o Definition of behaviors that are required to productively perform and live in space, promotion and maintenance of their occurrence within individual variability.
- o Development of a fundamental understanding of behavioral variability within individuals and creation of a data base containing complex behavioral and performance data.
- o Investigation of changes in perceptual functions (such as auditory localization, depth perception, body weight as a force, etc.), sensory sensitivity (threshold changes in color discriminations, tactile sensation, auditory levels, etc.), and sensory-motor interactions as they effect learning, adaptation, and discrimination in the space environment.
- o Determination of the relationship of biological rhythms, behavior, and performance.
- o Determination of how an individual's social and non-social environment influences his or her behavior so that performance and health of the individual may be maximized.

LIFE SUPPORT SYSTEM

Biochemical and Plant Studies

The following issues are listed in an order that approximates an increasing complexity of chemical and biological participation in a life support system. The ranking does not imply research priorities. In fact, investigations into any of the systems would provide highly important data for the development of life support systems destined for long-term, orbiting space flight. These issues denote areas of study that could be investigated in a two-week or short-term space flight. Other questions regarding basic plant physiology, such as nutrient uptake studies, are considered in the section on Gravitational Biology.

- o Investigation of photochemical and chemical systems in zero-g, in order to demonstrate photocatalytic and photoelectrochemical conversion of H_2O to H_2 and O_2 .
- o Investigation of the processes of non-photosynthetic microbial food production (such as methylotrophic yeasts) using chemically synthesized substrates or those available in the waste stream.
- o Study of the life supporting processes of O_2 production, CO_2 removal, and nitrogen cycle closure in a microbial, photochemically active system in zero-g, such as that provided by filamentous blue-green, nitrogen-fixing algae.
- o Evaluation of sensitivity of microbial cultures, such as algae, to changes in environmental parameters in zero-g, such as the amounts of O_2 and CO_2 , the intensity and frequency of light, and amount of nitrogen in the media.
- o Evaluation of the potential of hardy, cosmopolitan, edible plant species, such as onion, tomato, and lettuce, for use as food in a life support system in zero-g. In particular, characterization of their baseline plant growth kinetics in zero-g and determination of the conditions under which their growth is optimized.
- o Development of efficient means of growing higher plant biomass in zero-g, through such means as hydroponics. Are there advantages to propagating plants from tissue culture as opposed to seeds, in weightlessness?

System Studies

The following issues concern the design and development of waste management and food production systems in a weightless environment. Many of these issues are engineering problems which require the collaborative effort of biologists, chemists, and materials scientists.

- o Development of fluid handling and gas-liquid interchange methods for algal cultures and waste management systems in zero-g.
- o Development of a method for direct sunlight illumination of plant and algal growth chambers, in an orbiting spacecraft.
- o Management of transporting nutrients to the plants' root systems. In particular, design and verification of a water handling scheme in zero-g to bring in nutrients and carry off waste and excess materials. Follow-up of proven ground-based system designs by flying larger scale versions.
- o Study of the feasibility of using aerobic digestion and direct oxidation to convert organic wastes (such as cellulosic plant material, kitchen wastes, wash water, urine, and feces) to CO_2 and H_2O in zero-g.
- o Study of the feasibility of using an algal growth chamber in a closed environmental life support system for space station, by flying a large scale algal growth system on an STS mission.

BIOMEDICAL PROBLEMS

CARDIOVASCULAR AND CARDIOPULMONARY AREA

CARDIOVASCULAR DECONDITIONING

- o In-depth assessment of cardiovascular function both at rest and during stress tests using a variety of measurements at various stages of the space mission, immediately following weightlessness and continuing through the postflight phase. Included in this investigation is the development of improved non-invasive techniques to provide accurate and reliable hemodynamic measurements in humans under space flight conditions.
- o Determination of the relative contributions of blood volume loss and autonomic function changes in zero-g toward orthostatic intolerance.
- o Determination of the degree of cardiovascular deconditioning and its correlates with physiologic and other factors (environmental and behavioral) through a detailed analysis of inflight and postflight cardiovascular responses.
- o Prediction of susceptibility to orthostatic intolerance in the presence of space flight induced cardiovascular deconditioning.
- o Evaluation of changes in cerebral hemodynamics during reentry to assess the severity of orthostatic intolerance.
- o Study of the effect of repeated short-term exposures to zero-g on the time-course required for the space-flight induced cardiovascular changes to return to normal.

COUNTERMEASURES

- o Further development and testing of the existing types of countermeasures to cardiovascular deconditioning to confirm their effectiveness and to refine their patterns and means of use. Examples of putative measures are fluid and salt repletion, anti-g garments, lower body negative pressure, and physical exercise.
- o Formulation of experiments to test the utility of drugs and hormones as prophylactic or therapeutic countermeasures to orthostatic intolerance.
- o Clarification of the beneficial role of physical exercise during space flight.
- o Evaluation of the use of positive pressure breathing in conjunction with anti-g suit during reentry.
- o Development of alternate means to lower body negative pressure for stressing the vascular system of the lower extremities during weightlessness.
- o Development of measures to improve the reversal of space-flight induced cardiovascular changes following return to Earth.

INTERDISCIPLINARY ISSUES

- o Studies on decompression sickness and nitrogen washout.
- o Clarification of the relationships between cardiovascular and cardiopulmonary responses and changes in blood volume, red cell mass, and body fluid composition during weightlessness.
- o Study of the effect of changes in levels of circulating and excreted hormones on cardiovascular function.
- o Assessment of the degree of attenuation or exaggeration of cardiovascular response to zero-g by nausea and dehydration attendant to space sickness.
- o Direct determination of basal metabolic rates during weightlessness.
- o Assessment of the role of muscle atrophy in altered exercise capacity seen in zero-g.
- o Determination of the relative importance of physical inactivity due to both personal protective equipment and confined space environment versus weightless exposure in the induction of cardiovascular deconditioning.
- o Development of appropriate animal models suitable for studying the cardiovascular deconditioning process in weightlessness.

GENERAL PHYSIOLOGY

- o Elucidation of the effects of weightlessness on local regulatory mechanisms of the cardiovascular system through determination of absolute changes in venous capacity and venous compliance.
- o Characterization of the time-course of changes in central venous pressure and demonstration of the presence or absence of Gauer-Henry reflex.
- o Evaluation of the role low-pressure baroreceptor function in cardiovascular adaptation in zero-g.
- o Study of the influence of organ blood flow redistribution (renal, cerebral, lower-extremities) on cardiovascular adaptation to zero-g.
- o Study of cardiopulmonary adaptation in zero-g using measurements at rest and during exercise at various levels including the maximum.
- o Assessment of respiratory function changes in zero-g including changes in pulmonary blood flow distribution and blood gas tensions.

BIOMEDICAL PROBLEMS
BODY FLUIDS AND ELECTROLYTES

MAJOR PROBLEM AREA: LOSS OF BODY FLUIDS

- o Identification of mechanisms leading to acute loss of fluid and electrolytes, including characterization of headward fluid shifts, central hypervolemia, compartmental fluid volume changes, renal alterations leading to urine formation, alteration of plasma biochemistry, endocrine behavior related to fluid-electrolyte regulation, and associated circulatory disturbances. Utilize serial measurements where possible to characterize dynamic responses.
- o Identification of mechanisms affecting readaptation of fluids and electrolytes to terrestrial conditions upon return to one-g.
- o Assess fluid regulatory response and renal function using provocative testing such as fluid/salt loading, venesection, lower body negative (or positive) pressure.
- o During the more prolonged periods of space flight (the adaptive period following acute changes) clarify the hormonal, hemodynamic, and autonomic mechanisms which regulate fluid and electrolyte levels and determine whether the fluid volume and electrolyte losses become more or less severe.
- o Distinguish between volume and osmoregulation in the control of renal function during space flight.
- o Determine the factors which generate the changing plasma levels of the major hormones and electrolytes during adaptation to zero-g (major electrolytes: sodium, potassium, calcium, magnesium, chloride, phosphate; major hormones: ADH, aldosterone, angiotensin, renin, prolactin, prostaglandins, natriuretic factor, cortisol).
- o Determine the causes and consequences of the persistently elevated sodium and potassium urinary excretion levels previously observed in astronauts.
- o Determine if the non-renal quantities involved in metabolic balance of fluids and salts (i.e. thirst and diet, sweat, feces) are fundamentally disturbed in weightlessness.
- o Determine the effects of ancillary factors on the basic fluid responses to weightlessness, including the influence of fluid intake, dietary constituents, physical condition, gender, age, activity levels, and prophylactic drugs.
- o Collect the necessary data to validate ground-based analogs such as water immersion, lower body positive pressure, and head-down tilt, as appropriate maneuvers to investigate zero-g phenomena.

- o Development of appropriate animal models for conducting invasive studies in space and studying issues related to fluid-electrolyte biomedical problems.
- o Assessment of the increased risk of kidney stones during weightlessness, due to elevated serum calcium, and the effect of diet on this risk.
- o Determine if the adverse affects of body fluid losses (mostly encountered upon return to Earth) can be counteracted by such measures as fluid infusions, anti-diuretic agents, or inflight lower body negative pressure.

INTERDISCIPLINARY ISSUES

- o The contributory role of body fluid losses to orthostatic intolerance in general, and to the stresses of reentry and recovery in particular.
- o Possible contribution of central vascular congestion to motion sickness.
- o Determination if central hypervolemia is self-correcting or if its persistence could lead to impaired heart function.
- o Determine the role of the kidneys on calcium loss during space flight.

GENERAL PHYSIOLOGY

- o Characterization of the circadian patterns of fluids, electrolytes, and hormones during flight, with emphasis on determining if weightlessness produces a shift in these rhythms, and if so, what are their consequences.
- o Determination of the distribution of substances in various body compartments following entry into space.
- o Determine whether acid-base regulation is disturbed in weightlessness and if it plays a significant role in the adaptation process.

BIOMEDICAL PROBLEMS

VESTIBULAR

SPACE SICKNESS

- o Ascertain which factors are responsible for space sickness susceptibility. What is the source of tolerance in a resistant individual?
- o Determine whether an association between the symptomatology and time course of the space sickness disorder and physiological/environmental parameters can be documented.
- o Evaluate the currently conceived models of space sickness (i.e. sensory conflict, overstimulation of the vestibular end organ, labyrinth fluid imbalance).
- o Assess the contribution of neuronal reflexes and organ systems, other than the vestibular system, in producing the space sickness disorder.
- o Distinguish between the roles of weightlessness and head and body movements in contributing to the symptoms of space sickness.
- o Determine the relationship between sensory disturbances that provoke one-g motion sickness and the causal mechanisms of zero-g space sickness.
- o Can animal models provide measurable responses to low gravity and motion stimuli and serve as useful indicators of human responses?

COUNTERMEASURES

- o Is there a one-g maneuver for producing sensory disturbances analogous to those that provoke zero-g space sickness? Could this method be used for ground-based research, crew selection, and crew training?
- o Determine methods for enhancing parabolic flight-induced weightlessness as an analog to orbital flight and for studying resistance and susceptibility to space sickness.
- o Can efferent input into the vestibular apparatus and otoliths be manipulated in a manner that will tune out the mismatched sensory input?
- o Develop training programs that will prevent the occurrence of space motion sickness. Determine if training must be time-intensive (single sessions) or repetitive (multiple sessions) in nature.
- o Assess whether preflight habituation to motion sickness can be used to hasten inflight habituation and to ameliorate or prevent space sickness. What other measures can be taken to accelerate adaptation? Distinguish between habituation and adaptation.
- o Develop methods to reduce the severity of symptoms developed inflight.
- o Assess the efficacy of drug intervention for preventing or suppressing space sickness. Compare drug effectiveness in zero-g with that in one-g.

INTERDISCIPLINARY ISSUES

- o Determine if changes in labyrinthine function during space flight can be attributed to the effects of fluid shifts (or other circulatory factors) occurring, for example, in the endolymph, cerebral spinal fluid, and vasculature.
- o Assess whether the known processes of negative calcium balance and bone demineralization which occur in zero-g affect otolith function. What is the role of Ca^{++} in hair cell receptor potentials?
- o Evaluate the effect on the sensory input of deconditioned muscles belonging to the postural reflex arc.
- o Evaluate the effect of crew space sickness on workload, performance, crew behavior, and habitability.
- o Determine whether certain areas of the brain, such as the brain stem, cerebrum, cerebral cortex, diencephalon, and cerebellar regions, are critical to the development of space sickness, and correlate neuronal responses from these regions with those emanating from the vestibular region.

GENERAL PHYSIOLOGY

- o Characterize the development of the graviceptor systems and postural reflexes in weightlessness.
- o Determine the mechanisms by which space and gravity are perceived and integrated across sensory modalities to make normal postural and motion possible on Earth and in space.
- o Assess whether the vestibular system remains physiologically normal during space flight, such that key neuronal circuits and reflex pathways, neurochemical transmitter mechanisms, and anatomical components respond in zero-g as they would to stimuli in one-g.
- o Determine whether morphological changes in otoconial, labyrinthine, or neuroepithelial structures are associated with exposure to zero-g.
- o Evaluate the responses of the vestibular system in zero-g with respect to the roles of age, gender, and physical condition.

BIOMEDICAL PROBLEMS

HEMATOLOGY/IMMUNOLOGY

HEMATOLOGY

LOSS OF RED CELL MASS

- o Characterization/verification of the time course and magnitude of changes that occur in the erythropoietic system during exposure to zero-gravity including changes in: total blood volume, plasma volume, red cell production, red cell destruction, as well as changes in erythropoietin concentration and other controlling factors of erythropoiesis.
- o Determine if the observed decrease in red cell mass is: a normal zero-g adaptation process (self limiting), a transient response (self-correcting) to changes brought about by various flight related stresses, or a fundamental impairment of the red blood cell proliferation system.
- o Determine to what extent the observed decrease in circulating red cell mass is due to a decrease in production as opposed to an increase in destruction, and identify the underlying mechanism(s) responsible, including the assessment of factors such as: random hemolysis, erythrocyte shape changes, and membrane fragility that might cause an increased red cell destruction; or plasma volume shifts/hemoconcentration, changes in erythropoietin concentration, erythropoietin inhibitors, oxygen-hemoglobin affinity, blood flow, nutritional influences (diet, dehydration, space sickness) on bone marrow red cell production, ineffective erythropoiesis, or a altered sensitivity of marrow to erythropoietin which might cause a decrease in red cell production.
- o Identify the mechanisms affecting the readaptation of the red cell system to a one-g environment, including: the characterization of the time course of readaptation, the reversibility of inflight changes upon return to one-g and whether the repeated exposure of a subject to zero-g poses any potential health hazards.

GENERAL PHYSIOLOGICAL ISSUES

- o Evaluate the use of animal models (rodent, primate, or other small mammals) for extensive and invasive studies of human erythropoiesis control during space flight.
- o Determine if the stress of space flight alters the ability of the hematological system to respond to erythroid stresses such as hypoxia and venesection.
- o Determine what effects diet, stress, and weightlessness per se have on red cell proliferation.

- o Identify other red cell changes that take place during space flight (such as changes in morphology, function, metabolism, membrane characteristics and fragility) and the underlying causes and consequences of those changes.
- o Determine if the body's hemostatic mechanisms are altered during exposure to space flight, including: changes in platelet function, morphology, and kinetics and the relationship of platelets to bubble formation during decompression sickness.

INTERDISCIPLINARY/COUNTERMEASURES

- o Investigate the role that increased bone demineralization plays in the observed decrease in red cell mass including erythrosuppression due to such factors as: altered bone marrow function, calcium induced hormonal changes, and changes in local cellular factors that control hemopoiesis.
- o Determine if there is a relationship between space flight induced changes in red cell mass and space-flight changes in either protein or energy metabolism.
- o Determine the relationship between space-flight changes in non-erythropoietic hormones (such as calcium regulatory hormones, stress-related hormones, and growth or metabolic regulatory hormones) and changes that occur in the erythropoietic system.
- o Evaluate the affect of space flight induced alterations in the erythropoiesis system on human exercise performance (cardiopulmonary) during or after space flight and orthostatic intolerance postflight.
- o Determine the effectiveness of infusing red cells and/or plasma on reentry to provide either temporary or permanent relief for postflight orthostatic intolerance.
- o Evaluate the need for countermeasures to compensate for the decreased red cell mass and/or plasma volume.

BIOMEDICAL PROBLEMS

HEMATOLOGY/IMMUNOLOGY

IMMUNOLOGY

IMPAIRED IMMUNE RESPONSE

- o Determine the nature of the effect of space flight on innate and acquired immunity including: characterization of the time course and magnitude of changes that occur in differential leukocyte counts and immunoglobulin concentrations.
- o Determine if space flight produces a functional impairment in the ability of the immune system to respond to specific challenges including: changes in leukocyte function (chemotaxis, adherence, and phagocytic abilities), bone marrow leukocyte production, and B- and T-lymphocyte response to mitogenic challenges.
- o Identify the underlying mechanisms that are responsible for any observed space-flight related changes in the immune system including: alterations in cell proliferation due to weightlessness per se, or other stresses via hormonal and/or cellular mediators.
- o Determine if the effects of space flight on the immune system are completely reversible upon return to one-g, or if repeated space-flight exposures will produce cumulative effects that might compromise crew health in space or after return to one-g.

GENERAL PHYSIOLOGICAL ISSUES/INTERDISCIPLINARY ISSUES

- o Determine the effect that stresses other than weightlessness (diet, space sickness, launch reentry, EVA's, etc.) have on the immunological system including: studies of the kinetics of lymphocyte proliferation in weightlessness, the effects that varying gravitational environments have on lymphocytes, and the relationship of stress related hormones (corticosteroids, catecholamines, etc.) have on lymphocyte function and proliferation.
- o Evaluate which animal models of the immune system are appropriate for studying human immunological changes during space flight.
- o Determine if decreased bone demineralization has any effect on leukocyte proliferation inflight or postflight.

IMMUNOLOGY

ASSUMPTIONS

- o While no major changes have been shown to take place in the human immune system during or as a result of space flight, there have been a sufficient number of smaller immunological changes have taken place during zero-g to warrant a closer look into all areas of immunocompetence during space flight. However, at this point in time, these studies are probably of lessor importance than some of the issues in the other biomedical problem areas.
- o Work that needs to be done in this area includes: 1) identifying and/or documenting changes in the system: a) without secondary stresses and, b) under secondary stresses such as specific mitogenic challenges, 2) identification of the underlying mechanisms involved in any change, and 3) assessing the reversibility of any change after return to one-g.

BIOMEDICAL PROBLEMS

BONE/CALCIUM

BONE DEGRADATION

- o Characterization of the hormonal, renal, intestinal, and skeletal mechanisms that regulate plasma calcium levels and result in a whole-body loss of calcium during adaptation to zero gravity.
- o Determination of the factors that regulate the changing plasma levels of major electrolytes (calcium, phosphorus, and magnesium) and hormones (parathyroid hormone, calcitonin, and vitamin D) during adaptation to zero gravity.
- o Study of mechanisms leading to the ultimate degradation of bone, including characterization of the effects of changes in mechanical (tensile, compressional, shearing, and torsional) stresses, localized plasma volumes, and bone cell (osteoclastic, osteoblastic, and osteocytic) activity rates upon entry into zero gravity.
- o Identification of the major sources, such as muscle tissue, bone fluid, and/or hydroxyapatite, and sites of the whole-body calcium losses upon exposure to a zero-gravity environment.
- o Characterization of the effects of repeated space-flight exposure on bone and calcium regulation.
- o Characterization of the nature of change in bone and calcium metabolism upon return to Earth.
- o Characterization of the changes in bone density, strength, and cellular (osteoclastic, osteoblastic, and osteocytic) activity rates as inflight duration increases.
- o Determination of the causes and effects of the persistently elevated urine calcium excretion rates observed in the crewmembers of previous space-flight missions.
- o Evaluation of the influence of additional factors, such as age, gender, physical conditioning, exercise, dietary constituents, and drugs on the skeletal and calcium metabolic responses to weightlessness.
- o Study of provocative tests, such as calcium, phosphorus, and hormone infusions during zero-gravity to assess the efficiency of the calcium regulatory system in spite of the adaptative skeletal and calcium metabolic changes.

COUNTERMEASURES

- o Development of prophylactic and therapeutic countermeasure treatments to reduce or prevent the skeletal and whole-body loss of calcium during space flight.
- o Evaluation of phosphorus supplementation as a prophylactic and therapeutic countermeasure treatment for the skeletal and whole-body losses of calcium during space flight.

GENERAL PHYSIOLOGICAL ISSUES

- o Evaluation of animal models which are best suited for the study of human bone and calcium metabolism in zero gravity.
- o Characterization of the nature of the effect of space flight on phosphorus and magnesium metabolism and their relationships to the calcium metabolic changes.
- o Study of the acid-base balance during space flight and its influence on bone and calcium metabolic changes during space flight.
- o Study of neonatal and fetal bone development in a weightless environment.
- o Investigation of changes in the urine excretion rates of hydroxyproline as a reliable indicator of changes in bone resorption rates during space flight.

INTERDISCIPLINARY ISSUES

- o Characterization of the relationship of muscle atrophy and bone degradation during space flight.
- o Study of the influence of steroid (estrogen, glucocorticoids, prostaglandins, etc.) and general (growth hormone, insulin, thyroxin, etc.) hormones on bone metabolic changes during zero gravity.

BIOMEDICAL PROBLEMS

MUSCLE

MUSCLE ATROPHY

- o Determination of mechanisms, such as disuse, dietary deficiency, and alterations in glucose or protein metabolism, which are responsible for the decreases in muscle mass and strength during space flight.
- o Characterization of the changes in muscle cells and tissues in terms of structure, biochemistry, EMG, and strength during zero-gravity exposure.
- o Evaluation of the fast versus slow muscle tissues and postural versus non-postural muscle groups that are effected during space flight.
- o Determination of the relationship of dietary protein, protein metabolism, and muscle mass loss during space flight.
- o Evaluation of the relationship of caloric intake, energy expenditure, and muscle mass loss during space flight.
- o Characterization of the influence of physical conditioning, gender, and age on the losses of muscle mass and strength during space flight.
- o Evaluation of multiple exposures to zero-g on muscle tissue changes.

COUNTERMEASURES

- o Development of prophylactic and therapeutic countermeasure treatments such as exercise, caloric intake, and protein intake to prevent or reverse skeletal muscle alterations during space flight.
- o Evaluation of hormonal and other pharmacological treatments as effective means to reduce or prevent muscle atrophy during space flight.

GENERAL PHYSIOLOGICAL ISSUES

- o Evaluation of animal models which are best suited for the study of changes that occur in human muscles during space flight.
- o Study of cellular protein metabolic changes of muscle during space flight, including protein synthesis and breakdown and amino-acid pools and turnover rates.
- o Determination of time course and adaptive limits that occur during space flight if no countermeasures are applied.

- o Study of cellular changes in energy metabolism of muscle during space flight, including carbohydrate and lipid metabolism, and ATP production and utilization.
- o Comparison of the changes in muscle integrity, such as structure, strength, EMG, and biochemistry during space flight, disuse, starvation, and denervation.

INTERDISCIPLINARY ISSUES

- o Study of whole-body protein metabolism, including nitrogen balances, amino-acid pools and turnover rates, muscle catabolism, and dietary requirements, and its relationship to muscle loss during space flight.
- o Study of changes in whole-body carbohydrate and lipid metabolism such as energy expenditure, caloric intake, and glucose tolerance, and muscle atrophy during space flight.
- o Determination of the effect of endocrine (growth hormone, insulin, glucagon, testosterone, etc.) changes on muscle metabolic changes during space flight.
- o Evaluation of the influence of circulatory changes, such as headward fluid shifts, decreases in red blood cell mass, capillary volume, and oxygen delivery, etc., on changes in muscle mass during space flight.
- o Evaluate the relationship between zero-g muscle atrophy and fatigue.

BIOMEDICAL PROBLEMS

METABOLISM

CRITICAL ISSUES

Energy Regulation

- o Determine if the components of energy balance are altered during exposure to zero-g under carefully controlled nutritional conditions with accurate measurements of food and water consumption, activity, oxygen consumption, and carbon dioxide production. Is basal metabolism altered during zero-g? In particular, are the amounts of energy substrates metabolized appropriate to the energy demands in zero-g, or is metabolic efficiency altered?
- o Determine energy expenditure during both isotonic and isometric exercise in zero-g using measurements such as gross body composition, oxygen consumption and respiratory quotients, or turnover rates of body water to measure energy and material balance. To what extent does the body utilize carbohydrates versus fats as substrates for energy production during exercise?
- o Studies of glucose metabolism during weightlessness including characterization of insulin levels and production, free fatty acid and triglyceride levels, and other factors of carbohydrate and fat metabolism.
- o Elucidate the mechanisms involved in the observed sub-normal levels of plasma glucose and insulin under fasting conditions in zero-g. In particular, is the low glucose concentration due to increased peripheral utilization or decreased hepatic release of glucose?
- o Assess if ATP is generated from substrates and utilized during exposure to zero gravity with the same efficiency as during exposure to one-gravity.
- o Assess if the extraction and storage of the substrates glucose, non-esterified fatty acids, lactate, and amino-acids by the tissues of the body occur at normal rates.
- o Determine if anabolic and catabolic responses associated with energy and substrate mobilization function normally at zero gravity.
- o Evaluate the ability of energy regulating mechanisms to readjust to one-g conditions when required.

Protein Metabolism

- o Define and/or validate the changes that occur in protein metabolism during weightlessness including measurements of total body protein, nitrogen balance, as well as plasma concentrations and turnover rates of individual amino-acids.
- o Identify the mechanism(s) by which zero gravity alters body protein metabolism. In particular, is the negative nitrogen balance due to reduced protein synthesis or enhanced protein degradation?
- o Evaluate whether the negative nitrogen balance represents a zero-gravity adaptive phenomenon, or whether the negative balance represents a fundamental impairment of the nitrogen-accretive process.

Endocrine Changes

- o Characterize the "normal" endocrine response to weightlessness and space-flight stresses unrelated to gravity and determine how these responses affect the regulation of energy balance by hormones such as insulin, glucagon, thyroxine, cortisol, catecholamines and pituitary growth hormone.
- o Determine if inappropriate metabolic responses are due to altered hormone levels or from alterations in hormone receptors.
- o Determine the role of hormones (growth hormone, cortisol, etc.) and secondary hormonal mediators (for example, somatomedins) in the development of the negative nitrogen balance in microgravity.

GENERAL PHYSIOLOGICAL ISSUES/COUNTERMEASURES/INTERDISCIPLINARY ISSUES

- o Evaluate methods to minimize the negative nitrogen balance including measures such as changes in nitrogen (and/or energy intake), exercise, hormonal treatment (testosterone and pituitary growth hormone).
- o Identification of appropriate animal models of human energy balance and protein metabolism in order to perform more extensive and invasive metabolic studies.
- o Determine the minimal gravity force required to maintain normal body nitrogen metabolism.
- o Determine if muscle degradation is due to a fundamental change in protein metabolism rather than muscle disuse atrophy.
- o Determine the relationship between altered muscle and bone metabolism and space-flight changes in metabolic related hormones such as the pituitary growth hormone, cortisol, and others.

- o Evaluate the relationship between an altered metabolic demand and the observed flight decrease in red cell mass.
- o Assess disturbances in circadian rhythms in metabolic and hormonal systems during space flight, including an evaluation of characteristics of normal space-flight circadian rhythms. In particular, determine if there is a shift in the normal metabolic rhythms, an entrainment of a new work/rest cycle, or changes that could affect other physiological studies.

BIOMEDICAL PROBLEMS

RADIATION

- o Perform dose-response studies during space flight taking into account
 - the types of radiation involved in exposure - low or high LET (Linear Energy Transfer)
 - dose - low, medium, or high; single versus fractionated.
 - early, intermediate, and late biological effects - biochemical, cellular, and histologic changes; alterations in genetic material and in specific organs of special importance (the brain and the retina, for example); effects on life span of cells and animals.
- o Morphologic studies in animals to determine the extent of tissue damage resulting from exposure to radiation in space. Assessment of observed morphologic changes to determine if they have any functional significance in terms of organ dysfunction and/or decrement in performance.
- o Detection of functional changes using neurophysiological and behavioral testing techniques following radiation exposure in space.
- o Studies to determine possible synergistic, additive, or antagonistic effects of combining different types of space radiation with zero-g and other stress factors associated with space flight. Examples of such studies include evaluation of possible problems in cell proliferation kinetics under the combined (stresses of radiation and weightlessness, and studies of animal responses to combined) radiation and centrifugation in space, employing well-defined onboard radiation source.
- o Investigation of the biological effects of protracted and/or repeated exposures to H_2E particles in space.
- o Development of information and techniques for determining relative susceptibility of humans to the adverse effects of space radiation, taking into consideration age, sex, and other parameters.
- o Development of sensitive and reliable biological indicators which can be obtained inflight by acceptable means and which can be related to the degree of radiation exposure in space.
- o Development of sensitive techniques for detection and measurement of the effects of radiation exposure following space flight.
- o Determination of acceptable radiation exposure limits for personnel engaged in activities in space.
- o Research on the shielding problem and development of radiation protection standards.